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# DIETARY FACTORS AND HEPATIC INJURY*

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THE production of cirrhosis by dietary means alone[1, 2] afforded a new experimental approach to the study of liver disease. Realization that diet plays an important part in influencing the susceptibility of the liver to injury by toxic materials, is not a new development. In 1914 Opie and Alford[3] reported the influence of various diets on liver damage caused by chloroform poisoning, and numerous investigators have since studied this relationship.

In 1924 Fisher[4] and Allan, Bowie, McLeod and Robinson[5] observed independently that fatty livers occurred in depancreatized dogs maintained on insulin. It was shown that this condition could be prevented by adding minced pancreas to the diet. In a preliminary report Hershey[6] suggested and later Hershey and Soskin[7] demonstrated that crude lecithin could be substituted successfully for the supplement of pancreas. Best, Hershey and Huntsman[8] produced fatty livers in rats by feeding a diet of high fat content and showed that the deposition of fat produced in this way could be prevented by feeding purified lecithin. Best and Huntsman[9] subsequently found that the activity of lecithin was due to its constituent, choline. Casein was also shown by Best and Huntsman[10] to have a lipotropic effect. This action of protein was later shown by Tucker and Eckstein[11] to be due largely, if not wholly, to its content of methionine.

In 1935, Weichselbaum[12] noted that when rats were fed diets deficient in protein, and particularly low in the sulphur-containing amino acids, a poor growth rate, sickness and ultimately death resulted. At necropsy hæmorrhage into the liver was observed. Curtis and Neuburgh[13] had already found that the administration of excessive amounts of the sulphur-containing amino acid cystine produced "very extensive interlobular hæmorrhagic necrosis of the liver in rats, after 4 days on 8% casein, with 20% added cystine".

These investigations had been of relatively short duration and it remained for Chaikoff, Connor and Biskind[14] to report in 1938 that depancreatized dogs maintained with insulin for 2 to 3 years developed "hepatic fibrosis", or cirrhosis. In the following year during the course of investigation into the effect of vitamin B deficiencies in rats, Gyorgy and Goldblatt[1] produced cirrhosis in the intact animal. Chaikoff and Connor[2] also were successful in producing cirrhosis in dogs by feeding a high fat diet over an extended period.

A series of papers which appeared in 1941 showed conclusively that cirrhosis could be produced by feeding diets low in protein with or without a high fat content and could be prevented by adding choline to the diet. Methionine, a dietary precursor of choline, was also effective in retarding or preventing the cirrhotic process. These findings received widespread attention from clinicians, due to their possible significance in the pathogenesis and their application to the treatment of human liver disease.

Therapeutic use of the lipotropic factors in clinical practice is based on experimental results in which liver injury has been produced either by dietary means alone, by the administration of hepatotoxins, or by a combination of these two methods. Results of the experimental investigations must be analyzed carefully before an estimation of their applicability to clinical situations can be made. Before describing pertinent experimental work, some discussion of the processes involved in liver disease may be profitable.

*Cirrhosis.* — The stony-hard liver associated with dropsy was recognized by members of the

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Egyptian school of medicine. It was also described by Vesalius, by Morgagni, by Matthew Baillie and numerous later authors. Laennec first used the term "cirrhosis" to denote the tawny colour of the projecting nodules of liver tissue which are a feature of the disease. These he described as being of a "fawn or yellowish russet, bordering on the greenish". Such terms as "hob-nail liver", "gin-drinker's liver", "chronic interstitial hepatitis", "nodular cirrhosis", have been used to describe the pathological lesions or possible etiological factors of the condition. At present the term "cirrhosis" has been accepted fairly generally as descriptive of a condition in which are associated three definite processes: (1) Proliferation of connective tissue, interstitial, diffuse, or reticular. (2) Degeneration and death of hepatic cells. (3) Regeneration of hepatic cells.

Moon[15] has combined these three ideas in one sentence and has defined cirrhosis as a "progressive inflammation, diffuse in extent, accompanied by fibrosis, retrogressive changes in the parenchymal cells and proliferation of the remaining cells in the direction of regeneration." An increase in the fibrous tissue of the portal spaces is not in itself an indication of cirrhosis unless the lobular pattern is also distorted. According to Karsner[16] there is no reason to use the term as a synonym of "fibrosis" or "gliosis" and because of its special meaning, it should not be used with reference to any organ but liver.

Boyd[17] has pointed out that in distinction from other tissues which react to harmful stimuli by an inflammatory reaction, the characteristic reaction of the liver is by cellular necrosis. The regenerative power of hepatic tissue is very great, so that after removal of the noxious influence complete morphological repair can, and often does take place. If the harmful action is prolonged fibrous tissue may replace the damaged liver cells, the interaction of the two processes, liver cell regeneration on the one hand and fibrosis on the other, ultimately leading to "pseudolobulation" and distortion of the architecture of the whole organ. "In every instance in which the prolonged action of an agent has resulted in some degree of cirrhosis, the acute effects have been degeneration and necrosis of hepatic cells."[15]

Portal cirrhosis is accompanied by severe dislocation of the circulation. Kretz[18] using an injection technique, found that many nodules of hepatic cells were completely devoid of radicles of the hepatic or portal veins. Both central and portal veins were diminished in number and were located at the periphery of the nodules.

> "The radicles of both the portal and hepatic veins lie on the periphery of the lobule, and are embedded in stroma and proliferated tissue, which, as it contracts, produces obstruction of the portal venules. In such a liver the normal lobular pattern is obliterated and the architecture is altered. There are no longer lobules but only nodules of cells divorced more or less completely from normal circulatory relations."[15]

*Necrosis.*—Necrosis, as opposed to cirrhosis, implies simply a death of liver cells. This may be local, involving single cells or groups of cells in one part of the liver lobule, or it may be extensive, involving whole lobules or even whole lobes of the liver. In the latter case it is referred to as massive lobar necrosis. A characteristic of many liver diseases is that only part of the lobule becomes necrotic. Thus after the administration of carbon tetrachloride or of phosphorus the central portion of almost every lobule becomes necrotic. In certain diseases such as eclampsia, believed to be due to toxins produced in the body, the necrosis is lobular but peripheral in distribution. If recovery rather than death occurs after massive necrosis, the necrotic areas may become fibrosed, giving place to "post-necrotic scarring", or cirrhosis which resembles in appearance that produced in the more insidious portal cirrhotic process.

*Cirrhosis and necrosis of dietary origin.*—The publication of papers by Gyorgy and Goldblatt,[19] Daft, Sebrell and Lillie,[20] Webster[21] and Blumberg and McCollum,[22] almost simultaneously in 1941, established that cirrhosis could be produced by feeding synthetic diets low in protein. The feeding of diets high in fat, replacement of water in the diet with dilute alcohol, or the administration of large amounts of cystine, hastened the process, yet the amount of protein present apparently governed it. The addition of choline, which is of course present in normal diets, prevented the onset of cirrhosis even with these low protein diets. The preventive action of choline (and its precursor methionine) in experimental dietary cirrhosis has since been repeatedly confirmed. The factor governing the production

of cirrhosis appears to be the presence or absence of lipotropic substances rather than the level of protein intake *per se*. Choline plus cystine has been reported[24] to be more effective than choline alone. Under certain circumstances, when the organic sulphur of the diet is low, it is possible that cystine might alleviate this defect, sparing methionine for other essential purposes. If the organic sulphur supply is adequate, and the basal requirement for methionine itself is met, the addition of cystine with the supplement of choline would appear to be unnecessary.

The time required for dietary cirrhosis to develop varies with the circumstances. In one group of experiments the time necessary to produce cirrhosis in rats averaged less than three months, some animals becoming cirrhotic in as short a time as five weeks. Usually from 80 to 150 days are required. This contrasts with the production of fatty livers which have been observed in rats within a few days of starting the offending diet.

Descriptions of cirrhotic types of dietary liver injury have been given by Lillie and coworkers,[23] by Gyorgy,[24] by Himsworth and Glynn[25, 26] and by others. The nature of the lesions depends on the precise composition of the diet. In the gross, the surface of the liver may be discoloured and mottled, with a rough nodular appearance, but not infrequently the surface of the liver is relatively smooth and gives no indication of the degree of fibrosis actually present.

Microscopically, the earliest change evident, as would be expected, is the appearance of fat globules of varying size in the liver cells. A fibrosis reported to be mostly periportal commences later. Later still, the fibrous trabeculæ segregate nodules of fat-laden cells. Even in advanced cirrhosis it is possible to find apparently normal portal areas with duct, vein, and perhaps artery. In places, the trabeculæ broaden out into bulky areas replacing the hepatic parenchyma.

A most frequent finding in cases of experimental cirrhosis of dietary origin is the presence of globules of a peculiar hyaline, basophilic substance which takes up fat stains. The chemical composition of this material, called "ceroid", has not been discovered. Ceroid may also be found in the lung, spleen and other organs. Because ceroid apparently does not occur in human cases of cirrhosis but was present in the experimental disease, some investigators believed this was evidence that the two conditions are not comparable. However, when dietary cirrhosis without ceroid was produced experimentally in rats,[27] the discrepancy was removed. The nature and significance of ceroid is still unknown.

Daft, Sebrell and Lillie[28] were the first to report experiments which were interpreted to indicate the respective rôles of choline, methionine, and cystine in preventing dietary hepatic injury. They state that under their experimental conditions:

> "Choline (and methionine, a choline precursor) has a preventive action in the development of hepatic cirrhosis, and the sulphur-containing amino acids, methionine and cystine, have a preventive action in the development of hepatic hæmorrhage and necrosis. This suggests that the cirrhosis and the hæmorrhage and necrosis are separate and distinct entities."

The position of cystine in the choline-methionine-cystine triad is peculiar, inasmuch as when given as a supplement to various low protein diets it may aggravate hepatic cirrhosis. Quite recently, in 1944, Himsworth and Glynn[25, 26] have corroborated the conclusion of Daft *et al.* and extended its experimental basis. According to these authors:

> "Dietetic hepatic necrosis is a deficiency disease caused by a deficiency of a component of protein and prevented by administration of methionine." "Neither the carbohydrate, fat, vitamin, mineral nor choline content of the diet exert more than, at most, a modifying influence; the determining factor is the amount of protein eaten daily. . . ."

The massive hepatic necrosis observed by Sebrell's group and by Himsworth and Glynn has many points in common, clinically as well as pathologically, with acute yellow atrophy of the liver in man. The experimental disease may be fatal, or the animal may recover spontaneously without any change in the dietary regimen. In the latter case, the liver becomes heavily scarred and grossly irregular. In 1943 Hock and Fink[29] working independently in Germany with low protein diets (low in organic sulphur) made similar observations. The belief that massive hepatic necrosis is due to a deficiency of the sulphur-containing amino acids is thus backed by considerable experimental evidence. Nevertheless, this hypothesis cannot be accepted without reservation, since other workers have failed completely to produce massive necrosis in rats fed similar diets.[30, 31]

Rats which survive either the massive hepatic necrosis or its milder variant partial massive necrosis, develop jaundice, ascites and œdema. The liver becomes contracted, is firm, and may be considerably distorted with surface nodularity. Microscopically necrotic areas are replaced first with a cellular supporting tissue and later with fibrous tissue which assumes the wide band-like appearance so often seen in human nodular hyperplasia following subacute yellow atrophy. The liver cells also regenerate forming pseudolobules, irregular in internal arrangement and separated by bands of scar tissue. As in human cases, lobules least affected in the active stage of the disease show remarkable compensating hyperplasia.[26]

In contrast, in the development of cirrhotic lesions, a severe fatty infiltration is the most striking feature for the first 50 to 100 days. Necrosis of cells, if it occurs at all, is never marked. While some doubt exists as to where the fibrosis actually begins, thin bands of fibrous tissue are seen to extend from one portal area to another, cutting off groups of liver cells and dividing the lobules into smaller pseudolobules of varying size, thus finally producing the well-known appearance of Laennec's cirrhosis. Groups of cells separated by fibrous strands undergo proliferative changes still further obliterating the normal liver pattern. Bile duct proliferation varies considerably in degree in different animals and different parts of the liver.

Experimental cirrhosis produced with hepatotoxic materials such as carbon tetrachloride, presents an interesting variant which in its production may resemble human cirrhosis more than that produced by purely dietary means. With suitable dosage a Laennec type of cirrhosis can be produced. The progression of events resembles that described for the dietary (low choline) cirrhosis. However, gross fatty infiltration is less evident, while central lobular necrosis occurs in marked degree.

It is therefore possible to produce approximately the same end result, judging from the gross and microscopic appearance, in several ways. First, by feeding diets low in lipotropic factors or very high in fat, the liver cells may be kept loaded with fat for long periods, after which cirrhotic changes become apparent. Secondly, the action of chemical agents such as carbon tetrachloride, chloroform, phosphorus, arsenic or selenium, over a sufficient period produces a similar picture. Thirdly, massive liver necrosis (believed by Himsworth and Glynn to be induced by a deficiency of sulphur-containing amino acids especially cystine) if death does not occur, gives place to a post-necrotic fibrosis, often referred to as cirrhosis or nodular hyperplasia.

The views held by Daft, Sebrell and Lillie and corroborated by Himsworth and his associates on the production of massive lobar necrosis by feeding diets low in sulphur, have not been accepted without question. The administration of diets low in organic sulphur do not consistently produce massive necrosis as was mentioned earlier. In addition, Handler and Dubin[32] state that in the cirrhosis of choline deficiency, they have observed central necrosis of a focal nature. In their diets adequate cystine was present and the lesions were completely preventable by choline. From this they conclude that choline deficiency cirrhosis is itself a "form of post-necrotic scarring". It is, as they say, "difficult indeed to understand the development of scar tissue in a liver which is composed of living, albeit fatty, cells". In the general discussion of the pathogenesis of cirrhosis presented earlier, the consensus appeared to be that a replacement of dead or atrophied liver cells with fibrous tissue occurred, together with concomitant regeneration of remaining hepatic parenchymal cells. In the Banting and Best Department of Medical Research a number of experiments have been performed in which cirrhosis in rats was produced by feeding hypolipotropic diets. Sellers[33] and Hartroft[34] have not observed any actual necrosis of liver cells in such experiments. Radhakrishnarao[35] reports a similar experience. It is quite possible that in cases of mild injury continued over a long period, insidious fibrosis with little or no necrosis visible at any time may appear and in other cases, when the injury is severe, necrosis may predominate.

Even if the *processes* involved are similar, but differ in degree, the cause of massive necrosis appears to be something other than choline deficiency. Suspicion has attached in turn to diets low in organic sulphur, to a deficiency in tocopherol, or to a virus or bacterial infection.

The experimental evidence advanced to date is not sufficient to exclude completely any one of these explanations; in other words, while a relationship to low organic sulphur intake appears to exist, the *causal factors* remain unknown.

Not only may diets deficient in lipotropic factors give rise to hepatic injury independently, but there is experimental evidence that the lipotropes influence the susceptibility of the liver to various hepatic toxins. Miller and Whipple[36] depleted dogs of protein by plasmaphoresis and found that these animals had many times the sensitivity of normal dogs to chloroform poisoning. The increase in sensitivity could be abolished by feeding a high protein meal or by the administration of methionine or of choline plus cystine before or even 3 to 4 hours after the exposure to chloroform. It must be emphasized that these findings were made on protein-depleted or poorly nourished animals. Similar observations with respect to the protective effect of high protein diets or of methionine were made by Messinger and Hawkins[37] and Goodell, Hanson and Hawkins[38] in the case of mapharsen and arsphenamine poisoning. Sellards and McCann[39] have reported experiments with rhesus monkeys which indicate the possibility that the liver may be protected against a potent yellow fever virus by the oral administration of choline chloride. Drill and Loomis[40] showed that no extra protection against liver damage due to carbon tetrachloride was afforded by methionine supplements when the experimental animals (rats) were already receiving adequate diets. They have also reported[41] that in dogs no protection against carbon tetrachloride injury to the liver is given by methionine supplements when a low protein basal diet is fed. The small number of animals studied and lack of information about the previous nutritional status of the animals, makes it difficult to assess the value of this work.

It would thus appear that supplements of the lipotropic factors are effective in increasing the resistance against hepatic injury only when a deficiency of these substances exists in the diet. The "deficiency" in any one instance is, of course, influenced by such factors as growth rates, pregnancy, lactation, the presence or absence of pathological conditions and intake of other food substances. In the case of acute or chronic poisoning by certain toxic materials it is also possible that methionine may play a rôle in detoxification processes unrelated to its lipotropic activity. Furthermore, it must be realized that in assessing the clinical applicability of experimental studies, the nutritional requirements vary somewhat from species to species.

### Application to Etiology of Human Disease

The relationship of choline deficiency to human liver disease is obscure. A deficiency in the diet, a digestive defect, or impaired utilization of choline (or of its dietary precursor methionine) might all be of importance. Among the poor natives of India, Africa and China, who subsist on low protein diets, cirrhosis of the liver is extremely common. Cirrhosis has been found in approximately 30% of autopsies performed on male Bantus at the Johannesburg General Hospital. The diet of the Bantu is almost exclusively maize meal or "mealy meal", sometimes supplemented by fermented milk. It has been shown by Gilbert and Gillman[42] that rats fed on liberal quantities of this diet develop a multitude of lesions, among them cirrhosis of the liver. An analogy has been drawn between the occurrence of cirrhosis in chronic alcoholics and the experimental observations, previously mentioned, that the liver of animals on low protein, lipotrope-deficient diets, are abnormally sensitive to liver toxins, including alcohol.[43] Gyorgy[24] has drawn attention to the similarity between the lesions of lipotrope-deficiency and those of eclampsia and acute yellow atrophy. Numerous references in the literature are cited by Himsworth,[43] illustrating the fatal sensitivity of pregnant women to infective hepatitis. He suggests that the diversion of essential nutriments to the fetus at the expense of the mother may make the liver of the mother more susceptible to the toxic agent of infective hepatitis and predispose to massive hepatic necrosis. He has also referred to the relationship of high mortality associated with yellow fever vaccine jaundice in poorly nourished populations compared with the low mortality found in well fed groups. The analogy between these observations and the protective effect of methionine, or choline and cystine, on hypoproteinæmic dogs poisoned with chloroform, carbon tetrachloride, or arsenic, is easy

to draw. However, clinical reports on the *treatment* of acute infective hepatitis with lipotropic factors (especially methionine), have not been encouraging. Wilson, Pollack and Harris,[44] Hoagland and Shank,[45] Higgins, O'Brien, Peters, Stewart and Witts[46] have reported no particular benefit from its administration. While more favourable reports are available concerning the treatment of carbon tetrachloride poisoning and post-arsphenamine jaundice, the data are not convincing.[47, 48, 49]

In cirrhosis, Patek and Post[50] and Fleming and Snell[51] have reported favourable results using high protein, high vitamin diets. The presence of severe and protracted fatty deposition in the liver in experimental cirrhosis, and emphasis of this finding in early human portal cirrhosis by Connor,[52, 53] made therapeutic trials of pure lipotropic substances a logical step. Russakoff and Blumberg[54] reported in 1944 that choline could be used clinically as a successful adjuvant to the treatment of cirrhosis. Among a number of other reports available, a recent one is that of Beams.[55] In eight cases with enlarged livers, in which fatty infiltration was suspected, a choline, cystine and yeast supplement was added to a high protein, low fat diet. Seven of the eight cases responded more quickly and more satisfactorily than did fifteen similar cases treated with the same diet but without the choline-cystine supplement. Patients with livers which were not enlarged, showed no response to the therapy. Beams points out that a high protein diet if tolerated would probably supply the necessary lipotropic factors. Often they could not be supplied by diet alone because many patients could not tolerate large amounts of food.

Partly due to the inherent difficulties of controlling clinical studies adequately and partly to the fact that the basal diets used in these studies themselves usually contained large amounts of the lipotropic factor, the results of clinical investigations are difficult to assess.

### Repair of Experimental Cirrhosis

It is well established that in animals in which cirrhosis has been produced by chemical agents, recovery of the liver lesions may occur when administration of the toxic substance is stopped and a normal diet is supplied. Cameron and Karunaratne[56] observed that cirrhotic livers produced by carbon tetrachloride regained a normal appearance when administration of the toxic agent was discontinued. Edwards and Dalton[57] also had shown that when normal diets were administered to cirrhotic mice, the liver parenchyma was considerably restored within a month, although fibrous tissue and reticulum could still be demonstrated by appropriate staining methods.

Lowry, Ashburn, Daft, Sebrell and Lillie[58, 59] reported that replacement of choline in the diet of rats with dietary cirrhosis resulted in the disappearance of fat from the liver cells, a marked increase in size, and apparently in number of cells, with the formation of hyperplastic nodules. Disappearance of the excess fat occurred in 16 to 18 days.

In order to assess the value and relative importance of the lipotropic factors in treating cirrhosis produced with carbon tetrachloride, experiments were performed on cirrhotic albino rats by Sellers, Best and Lucas.[60] Young adult rats in which a moderate degree of cirrhosis had been produced by the administration of carbon tetrachloride, were placed on a basal hypolipotropic diet supplemented in the case of different groups with choline, methionine, proteins (containing varying amounts of methionine), and inositol. The animals receiving the hypolipotropic ration alone showed no improvement in the cirrhosis; indeed, fat deposition in the liver increased, degenerative renal changes occurred and most of the rats in the group died within three weeks.

When adequate amounts of choline or methionine were added to the diet a remarkable improvement in the gross appearance of the livers occurred within two to three weeks. After three months the livers appeared normal and when examined microscopically it was usually necessary to use special stains to demonstrate an increased deposition of fibrous tissue. Although a high protein diet which contained an adequate amount of methionine produced results of a similar favourable nature, a high protein (35%) diet with a relatively low methionine content was not as beneficial as a ration containing 20% of similar protein to which supplements of choline or methionine had been added.

No evidence was secured that inositol exerted a favourable effect on experimental cirrhosis. The experiments indicated that the lipotropic agents were essential for repair processes but

did not suggest that adding additional amounts of choline or methionine to diets already containing adequate amounts of these substances would enhance the therapeutic effect, unless some interference with the absorption or physiological action of the lipotropic factors existed. These authors do not minimize the importance of administering a diet adequate in caloric value, in vitamin and mineral content, but suggest that the favourable results obtained in treating patients with liver damage with "effective therapeutic diets" may be attributable in large part to the lipotropic factors present in such rations.

## SUMMARY

1. Cirrhosis can be produced consistently by prolonged feeding of diets low in choline and its precursors. There is acceptable evidence for regarding dietary cirrhosis as a choline-deficiency disease.

2. Massive lobar necrosis has been produced in some laboratories by feeding to rats diets low in the sulphur-containing amino acids. This is not a consistent finding, and the relationship of methionine and cystine to the disease is not entirely clear. At present their lack must be regarded as a contributory rather than a causal factor.

3. A remarkable degree of repair may take place in experimental cirrhosis produced by carbon tetrachloride. Choline or its precursors are necessary in the repair process. There is no evidence that combinations of the lipotropic factors, or increased total intake of these substances, cause a greater degree of recovery than the presence of an adequate amount of a single lipotropic factor in an otherwise adequate diet.

The author has been fortunate to have the opportunity of discussing the subject matter and text of this review with Professors C. H. Best and C. C. Lucas. These discussions have been both helpful and instructive.

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## RÉSUMÉ

Revue des travaux récents concernant le rôle de la nutrition dans les lésions hépatiques. Il est possible de produire régulièrement une cirrhose par l'usage prolongé d'un régime carencé en choline et en certains corps servant à la synthèse de celle-ci. Par ailleurs, la carence alimentaire en acides aminés soufrés (cystine et méthionine) est capable de déterminer une nécrose lobaire massive du foie des rats. Le tétrachlorure de carbone peut également causer la cirrhose; mais celle-ci peut manifester une certaine restitution, grâce à l'usage des substances lipo-tropiques nommées plus haut. Une fois ces substances présentes en quantités suffisantes dans le régime, l'usage de quantités plus fortes ne permet pas d'obtenir une restitution plus parfaite. Importance des protéines alimentaires, et spécialement des protéines riches en cystine et en méthionine, dans le traitement des maladies humaines comportant des lésions hépato-cellulaires. PAUL DE BELLEFEUILLE

# INTRAVENOUS ETHYL ALCOHOL IN THE TREATMENT OF STATUS ASTHMATICUS IN CHILDEN*

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ALCOHOL administered intravenously is a comparatively recent innovation. Marin[1] in 1929 first recommended that ethyl alcohol be used intravenously for general anæsthesia. However, it has had only sporadic use and then in conjunction with other anæsthetic agents. In 1939 Mueller[2] emphasized its benefits as a rapid source of food and energy and as a sedative. In 1945 Moore and Karp[3] reviewed its various applications in the treatment of the surgical patient. However, it was not until 1947 that Brown[4] first suggested that it might be valuable in the treatment of status asthmaticus. He reported that 5 out of 6 cases with severe bronchial asthma who did not respond to the usual medications were effectively relieved by intravenous ethyl alcohol. To the best of our knowledge, these were all adults, and there have been no reports of its use in children.

Ethyl alcohol acts on the central nervous system and produces at first a feeling of well-being and of loss of anxiety in the patient. With increasing amounts, there is a stage of excitement and then of sleep. Analgesia soon follows the latter, and with an excess, unconsciousness will occur, which if allowed to persist for 10 to 12 hours, ends in death.[6] While it is generally agreed that there is no depression of the respiratory centre, except at a late stage of alcohol poisoning, the extent to which it is stimulated is debated.[6, 9, 10] Higgins[8] showed that after the oral administration of alcohol, there was no broncho-constrictor action and seldom any broncho-dilatation. Alcohol causes an increase in pulse rate and a vasodilatation but has a minimal effect on the blood pressure. It is rapidly and almost completely (90 to 99%) oxidized in the body to carbon dioxide and water. One gram of alcohol yields seven calories. Hence, it supplies nourishment and can replace fats, carbohydrates or proteins as a source of energy.[2]

The toxic dose of alcohol is 7.7 c.c. per kg. of body weight. Analgesia and sleep are produced by 1.5 to 3 c.c. per kilo.[7] When given intravenously, there are no after-effects, such as acidosis, headache, nausea or vomiting, which may follow an equivalent amount taken by mouth.[2] Alcohol can be given to children in relatively larger quantities than adults without danger.[6] It is only with the higher concentrations (10 to 30% of alcohol) that such complications as hæmolysis, shock and decreased urinary output have occurred. Sclerosis of vessels occasionally occurs with a 5% solution but this is rare, particularly if the alcohol is followed by a small infusion of saline.[3]

The material is prepared by adding 50 c.c. of 95% ethyl alcohol to 1,000 c.c. of 5% glucose in saline. Hence, in the final solution, there is a 5% ethyl alcohol content.[4]

As indicated by Brown,[4] we thus have a solution which is non-toxic and non-allergenic. It acts as a sedative without having the undesirable side-effects of adrenalin and aminophyllin, and furthermore, is effective in cases where the latter have failed. It is, if anything, a respiratory stimulant, not a depressant, and causes vasodilatation and possibly broncho-dilatation. It supplies electrolytes and readily available calories (50 gm. of glucose is equivalent to 200 calories and 50 grams of alcohol to 350 calories, giving a total of 550 calories). These are all imperative in the treatment of a tired, anxious, hungry, dehydrated patient, in acute respiratory distress.

### CASE 1

C.H., female, aged 2 years, weight 10 kilo. This child has had eczema since the age of 2 months and asthma since the age of 18 months. Her first attack of asthma occurred in August, 1947, and followed an upper respiratory infection. She had a severe attack in October, 1947, which required admission to hospital and was relieved after one day, using adrenalin subcutaneously and oxygen by inhalation. She had 4 or 5 attacks at home following this episode. A sinusitis was considered to be an important etiological factor in her condition and she was treated for this in the Ear, Nose and Throat Clinic.

Her last attack began on February 10, 1948. She was given ephedrine orally, an aminophyllin suppository, and adrenalin by inhalation at home, with no improvement. She did not eat all day and by evening was completely exhausted and admission to hospital was recommended by the family doctor. She was given 0.3 c.c. of adrenalin subcutaneously on arrival with considerable relief. During that night, she was given 16 milligrams of phenobarbital by mouth and received

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adrenalin 0.1 c.c. subcutaneously on four occasions. She was found to have an upper respiratory infection which presumably precipitated this attack of asthma and was treated for this with penicillin intramuscularly. On the morning of February 11, she was still having her acute asthma. Hence, we had a child in status asthmaticus who needed rest, food and relief from her acute respiratory distress, which was not responding to adrenalin. Intravenous ethyl alcohol therefore seemed indicated here. The child was given 50 c.c. of the solution in the first 15 minutes, then 350 c.c. during the next 7½ hours. Within 10 minutes after starting the intravenous administration, she fell asleep and after one hour her respiratory rate dropped from 60 to 48 per minute and her breathing was much easier. At 2 hours there was no audible wheezing. She was awake but drowsy and coughed frequently. In the last hour she was given 100 c.c. and she fell asleep shortly after. On auscultation of the chest it was noted that the expiratory phase was still prolonged but the rhonchi had decreased greatly. She slept throughout the night without further medication and in the morning had no respiratory distress, and on auscultation no rhonchi were heard.

### CASE 2

M.S., female, aged 10 years, weight 31 kilo. This patient was perfectly well until 17 months prior to admission, when she began to have periodic attacks of asthma. She was followed at another hospital and when her last attack started, two days prior to this admission on January 20, 1948, she was referred to the Children's Memorial Hospital. She was treated for 2 days with adrenalin and the attack subsided. On investigation it appeared that a bacterial allergy with bronchiectasis as the probable focus of infection was the etiologic factor. While in hospital, on January 29, she developed another attack of asthma, which was not relieved for 24 hours, despite six injections of adrenalin. In view of our experience with the first case, again ethyl alcohol seemed indicated.

She received 200 c.c. of the glucose alcohol solution within 1 hour and 15 minutes, and then 800 c.c. during the next 10 hours. After 15 minutes she was breathing more easily and felt subjectively better. She felt drowsy but did not sleep. Improvement was gradual and she coughed frequently. She slept that night without further medication and the following morning was up and around the ward. However, on auscultation, a few rhonchi could still be heard posteriorly.

### CASE 3

H.N., female, aged 8½ years, weight 24 kilo. This child had eczema in infancy and her first attack of asthma occurred at the age of 1½ years. These have recurred about once a month since that time without any apparent predisposing cause. On investigation, she was found to be sensitive to various foods and inhalants. Her last attack began on March 14. After 2 days at home she was brought to the out-patient department, where she was given 0.3 c.c. of adrenalin subcutaneously. She did not respond at all to this medication and admission to hospital was advised. During the next 5 hours the above dose of adrenalin was repeated twice and she was kept in an oxygen tent. However, the acute respiratory distress persisted, so that it was decided to give her intravenous ethyl alcohol.

She received 80 c.c. of the glucose alcohol in the first 10 minutes and the remaining 920 c.c. in 6½ hours (40 to 50 drops per minute). She fell asleep after 15 minutes but woke up ½ hour later, feeling drowsy, subjectively improved and coughing, but with less dyspnœa. She remained in this state for the next 5 hours and then fell asleep again till the morning. She required no other medication during the night. On the morning of March 17, three days after the onset of the asthma, she was taken out of the tent and had no apparent respiratory distress. However, on auscultation, the expiratory phase was slightly prolonged and a few scattered rhonchi could be heard, especially at the bases.

She was found to have a sinusitis and a minimal right basilar pneumonia, which undoubtedly precipitated this attack. These responded to sulfadiazine and penicillin and the child was discharged on March 24, 1948, without recurrence of her acute asthma.

## DISCUSSION

From these three cases it is apparent that this method of therapy was effective in overcoming the acute asthmatic state where adrenalin subcutaneously had failed. Furthermore, on the day following treatment, their chests were much clearer to auscultation than is usually found following treatment with adrenalin. It is interesting that in each of these children frequent coughing was noted during the administration of the alcohol, and that they were able to expectorate some of the thick, stringy mucus. In the three patients presented, the attack of asthma was precipitated by an infection. This is frequently the case in children and hence it is very important to begin chemotherapy or antibiotics immediately.

It has been emphasized by Brown and others[5] that the first part of the solution must be given rapidly in order that the alcohol may have its full effect. With this in mind, and from our own experience, we suggest the following routine. The total amount of solution required is calculated on a basis of 40 c.c. per kilo of body weight, that is, 2 c.c. of ethyl alcohol per kilo. The first 80 to 100 c.c. of the solution is given intravenously in the first 10 minutes, that is, at a rate of 120 to 150 drops per minute. The remainder of the solution is given at the rate of 2 drops per kilo per minute. In infants particularly, the total amount of solution may be limited by their tolerance for saline. In these cases we suggest that the amount of saline required for maintenance[11] be calculated and that an equal amount of the above solution be given. The remainder of the alcohol can then be given as 5% ethyl alcohol in 5% glucose in distilled water.

## SUMMARY

1. A brief review of the literature on the use of intravenous ethyl alcohol has been presented.

2. The physiological action of ethyl alcohol has been discussed.

3. The successful use of intravenous ethyl alcohol in the treatment of three children, aged 2, 8½ and 10 years, with status asthmaticus, has been described.

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# TWO FATAL CASES OF BOTULISM FROM HOME-BOTTLED ASPARAGUS*

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ABOUT thirty years ago, Glancy[1] described in this *Journal* the first, and, to date, the largest outbreak of botulism to be recognized in Canada. Dubovsky and Meyer[2] in 1922 reported having isolated strains of *Clostridium botulinum*, types A and B, from 27 of 100 soil samples collected from various parts of Canada. Yet the disease has apparently been rare in this country, and not until recently was there any record of the causal micro-organism having been identified in a human botulism episode in the Dominion.

In 1947, we[3] reported three fatalities from botulism at Nanaimo, B.C., due to home-canned salmon. *Clostridium botulinum*, type E, was isolated from companion tins of salmon and chicken, and from a sample of nearby garden soil. This raised the total number of Canadian outbreaks of human botulism to four, involving 34 persons, 19 of whom died. These figures must now be adjusted to include two additional fatalities which occurred recently near Grand Forks, B.C., from consumption of home-bottled asparagus contaminated with *Cl. botulinum*, type A.

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Based on a paper presented to the Epidemiology Section at the Annual Meeting, Canadian Public Health Association, Vancouver, May 18, 1948.

*Epidemiological and clinical data.*—Just before noon on February 23, 1948, a farmer had a hurried lunch with his wife, aged 57, and his daughter, aged 28. The parents were Czechs by birth, and emigrated to Canada in 1913. The farmer had recently recovered from influenza, but otherwise all three were in good health. The meal consisted of soup, veal, potatoes, asparagus, bread, cake and tea. The man had fetched a bottle of asparagus from the basement at his wife's request. After warming the contents in a frying pan, she had served a helping to each person, and poured the remainder into a dish which was placed on the table. The man was a light eater, and did not have a second helping of asparagus; but the women were both heavy eaters, the wife weighing 260 lb. The farmer then left for a short trip into town, had several glasses of beer on arrival there, and after transacting his business, returned home around 3 p.m.

After breakfast next day, the wife complained of a pain in her side, but this was not considered unusual, since there had been a kidney operation about two years previously. Although malaise persisted throughout the day, she was able to prepare meals for her husband and herself, and went to bed at 9 p.m.

The daughter, who had left home the night before to return to work at a hotel in town, had a bad headache on rising that morning. She managed to continue working, despite malaise, until the late afternoon, when she felt too "shaky" to carry on, and was driven home, arriving there at 10 p.m. Her mother got up and put her daughter to bed, but stated casually to her husband that she herself might feel better if she could have her stomach pumped out. Both women slept during the night, but the elder was very restless, and when her husband got up at 6 a.m. on the 25th, she admitted being seriously ill. The farmer went outside to do a few chores, and noticed several chickens sitting on the roost "as if they were drunk". On his return the daughter was awake, and also complained of being very sick, so he sent for a doctor.

At about 7.30 a.m. the doctor arrived, and found the two women dizzy and weak, but with normal temperatures. The daughter complained of pain in the back of her head, difficulty in raising her head off the pillow, inability to eat "as her throat was sore", and nausea. She had vomited during the night. The mother com-

plained also of difficulty in breathing. In view of the man's recent influenza, the doctor thought the women had contracted this infection, and prescribed accordingly. No particular examination appears to have been made for ptosis, diplopia, or other characteristic evidence of cranial nerve involvement.

Their condition rapidly worsened during the morning. For breakfast, they took a few sips of coffee from a cup; by noon they could only sip water from a spoon. At 1 p.m. their condition was so bad that another doctor was sent for, who on arrival half an hour later said there was nothing he could do for them. Both women were very short of breath, and markedly cyanosed, just before death. The mother died soon after 2 p.m. and the daughter 20 minutes later, *i.e.*, about 50 hours after eating the asparagus. Throughout the morning, the sick chickens, some 10 in all, had also died.

At autopsy, no signs of disease were noted, nor was there any evidence of poisoning. Samples of vomitus and gastro-intestinal contents, and various organs, were sent to the Provincial Analyst at Victoria for chemical analyses, with negative findings. Two of the dead chickens were also forwarded for examination, with similar results. The crops of three dead chickens cut open by the local police contained a quantity of mash of a greenish colour, which was tentatively ascribed at the time to asparagus.

*Bacteriological examination of home-bottled asparagus.* — A bacteriological examination of the stomach contents of the younger woman, made at the Royal Jubilee Hospital, Victoria, resulted in the isolation of an anaerobic micro-organism. This was sent to the Provincial Laboratories in Vancouver for identification, and turned out to be *Cl. welchii*. However, since the information accompanying the specimen suggested botulism as the possible cause of death, the police were requested to forward any home-canned foodstuffs found on the premises where the fatalities occurred.

A consignment of foodstuffs was received on April 3, 1948, comprising two sealers of meat, one of string beans, two of corn, one of corn on the cob, one of tomatoes, and three of asparagus. On removal of the lids, all the bottles appeared tightly sealed, except one of meat, and the three of asparagus. The meat was contaminated, but not with pathogens. The findings on the three asparagus bottles were as follows:—

*Bottle 1.*—Contents very malodorous, juice turbid, signs of slight gas formation, and pH 7.3. Gram stain of juice showed only Gram-positive bacilli, with oval spores. About 1 c.c. of the juice was inoculated directly into cooked meat medium. After incubation at 37° C. over a week-end, the growth was examined microscopically, and streaked on to blood plates which were incubated aerobically and anaerobically. These procedures yielded a pure culture of a Gram-positive, sporulating anaerobe, resembling *Cl. botulinum* in morphological and biochemical properties. The first culture filtrates from this strain, and likewise 1 c.c. amounts of the asparagus juice from the bottle, failed to kill mice. However, on repeated subculture, the strain became toxigenic, yielding filtrates of potency up to 1,000 mouse M.L.D. of type A toxin per c.c.

*Bottle 2.*—Contents slightly less malodorous,* no turbidity, and no apparent gas formation, with pH 7.2. A pure culture of a micro-organism apparently identical with the foregoing in morphological and biochemical characteristics was isolated by the same techniques. Culture filtrates initially prepared therefrom contained up to 10,000 mouse M.L.D. per c.c., and by antitoxin neutralization methods, the organism was identified as *Cl. botulinum*, type A. The asparagus juice from this bottle contained 250,000 mouse M.L.D. per c.c. of the type A toxin.

*Bottle 3.*—Contents normal in smell and appearance, with pH 5.6. An anaerobic, spore-bearing bacillus was isolated, but it was not *Cl. botulinum*.

*Cl. botulinum*, type A, was therefore present in apparently pure culture in two out of three bottles of asparagus. A similar strain was isolated in pure culture from the soil of the asparagus bed, and yielded a toxin of more than 50,000 mouse M.L.D. per c.c.

## DISCUSSION

These two deaths from botulism bring the number of outbreaks recorded in Canada to five, with 36 persons affected, 21 fatally. These figures are still very low by comparison with the United States incidence, which Meyer[4] has estimated at a minimum of 463 outbreaks, involving 1,253 persons, with 816 deaths, over the period 1899 to 1947. It is difficult not to conclude that some part of this disparity is more apparent than real, and that botulism at times strikes unrecognized in Canada. One of our main purposes in reporting this episode in such detail is to alert physicians to the perils of botulism, rare though it may be. In both the Nanaimo and the Grand Forks outbreaks, the correct diagnosis was initially suggested by the laboratory on clinical and epidemiological grounds—a fact which could be interpreted as further evidence of the need for more complete coverage of the country by good public health laboratory service, but which also indicates that the practitioner is not prone to recognize and verify the striking symptoma-

* The contents of bottles 1 and 2 had an odour resembling that of laboratory-grown cultures of *Cl. botulinum*.

tology of this disease. In the Nanaimo episode, poliomyelitis was tentatively considered, while at Grand Forks the provisional diagnosis of influenza was changed to possible arsenical poisoning after the patients had died.

Another lesson to be drawn from these fatalities is the need for continued education of the public in home-preservation of foodstuffs. The farmer recalled having helped his wife perform the bottling around the beginning of June, 1947, *i.e.*, about nine months prior to the fatalities. The asparagus had been brought in from the field, washed, placed in an open kettle on the stove, and boiled until "cooked through". The bottles were just washed in warm water by the woman, the asparagus filled into the bottles, and the tops put on by the man. There was no subsequent heating. This almost unbelievably casual technique obviously afforded plenty of opportunity for contamination from soiled fingers during filling and capping of the bottles. Apart from this, the strain of *Cl. botulinum* isolated from two of the bottles was found to survive the temperature of a boiling water bath for at least half an hour, thus indicating that spores originally adherent to the asparagus could easily have survived the temperature to which they were subjected. In view of the very slovenly bottling process, it is rather astonishing that *Cl. botulinum* should have been present apparently in pure culture in only two of the bottles. Another curious fact is that despite the close similarity between the two strains isolated, the juice in one bottle was non-toxic, while that in the other was extremely toxic; but such findings are not unusual.

Two points, *viz.*, the death of the chickens, and the farmer's escape from botulism, may be readily explained, although on circumstantial evidence only. The man recalled having let the chickens out of the run as he left home after the fatal lunch. They were apt to stay around the house, and his wife customarily fed them scraps from the household meals. If the contents of the bottle opened for this meal were as toxic as those of Bottle No. 2 above, relatively very small amounts of asparagus might have sufficed to kill the chickens. The man's failure to contract botulism may probably be ascribed to his comparatively small appetite, and to the fact that his portion may have been heated to a higher temperature in the frying pan. The alcohol in the beer consumed shortly after the meal is not likely to have had any marked prophylactic effect. After he had left, the women perhaps ate the remaining asparagus, some portion of which may not have been even warmed in the pan. Another possibility is that they had tasted the asparagus on first opening the bottle, before it was warmed; for the husband stated that his wife's preserved foodstuffs had frequently gone bad, and she was in the habit of tasting them before serving.

## SUMMARY

1. Two deaths from botulism occurred on a farm near Grand Forks, B.C., early in 1948.

2. *Cl. botulinum*, type A, was isolated from two bottles of asparagus, put up very unhygienically on the farm some nine months previously. A similar bottle of asparagus had been consumed about 50 hours prior to the fatalities.

3. The condition was not diagnosed clinically, despite the clue afforded by several chickens dying with paralysis.

4. The total of recorded outbreaks of botulism in Canada now stands at 5, with 36 persons in all affected, including 21 fatalities.

5. The causal micro-organisms (types E and A respectively) have been isolated in only two of these outbreaks, both of them occurring in British Columbia within the past four years. In each instance, a homologous culture was isolated from nearby garden soil.

We desire to express our appreciation to Dr. R. G. D. McNeely, Director of Laboratories, Royal Jubilee Hospital, Victoria, for having first brought these fatalities to our attention; to Sergeant E. F. McKay, i/c Grand Forks District, British Columbia Provincial Police, for most helpful co-operation; and to Dr. K. F. Meyer, Director, Hooper Foundation, University of California, and his colleagues, for many favours.

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The most benumbing thing to the intellect is routine, the most bewildering is distraction; our system is a distracting routine.—Walter Bagehot.

# THE VISCERAL MANIFESTATIONS OF DISSEMINATED LUPUS ERYTHEMATOSUS*

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DISSEMINATED lupus erythematosus has long been known to exhibit widespread visceral lesions, resulting in numerous and varied signs and symptoms. The original manifestation of the disease may be a lesion of the skin. The diagnosis in such an instance is comparatively easy but when it is recalled that the presenting symptom of the patient may be "arthritis", fever, pleurisy, lymphadenopathy, urinary abnormalities, etc., it at once becomes obvious that the patient will seek aid from the general physician rather than from the dermatologist.

## General Features

1. *Incidence.*—Proved cases are not frequent even in the records of large general hospitals. At the Vancouver General Hospital our 11 patients were diagnosed in the past 3½ years, and these form the basis of this report.

2. *Age.*—The disease commonly occurs in the third decade of life. One case has been described in a 5 year old boy.[1] In a review of the literature up to 1931, 4 were found under 15 years of age.[2] In a more recent series 7 out of 30 were under 14 years.[3] In our group the youngest was 17 years, the oldest 49 years; 6 were in their 20's.

3. *Sex.*—Females are most commonly affected, in the ratio of about 5 females to 1 male.[1, 3, 4] One of our 11 cases was in a male.

4. *Duration.*—The disease is variable in its duration. The onset is usually insidious, and the course may be marked by remissions and exacerbations. The remissions may last months or more. In some patients it runs a rapid, fulminating course. In two series[3, 4] the shortest course was 3 months and the longest 6 years. In our group the average duration between onset of symptoms and death was 20 months. The shortest was 5 months; the longest was 3½ years. All except one case were followed until termination. The later course of this one patient is not known.

## General Metabolic Changes

As a general background there may be an indefinite history of vague ill health, malaise and possibly some loss of weight. Fever develops and becomes a persistent, prolonged feature of the disease. The fever is remittent in type; it is quite high and sustained during the acute phases. It is accompanied by chills or chilliness and profuse sweats. In 2 of Mook's[4] 13 cases, however, fever was absent or insignificant. There is a proportionate increase in the pulse rate. Progressive malaise, prostration, marked weight loss and finally, if the disease is prolonged, cachexia occurs.

All of our cases had a marked fever which in the earlier stages of hospitalization was variable in its course, but which as the disease progressed became high, remittent in type, spiking up to 103 to 105 degrees. The fever was frequently accompanied by chills and profuse sweating. In the cases under our observation it was noted that the patients did not appear nearly as ill as their temperature would indicate in the earlier stages. Moderate loss of weight (8 to 10 pounds) was usual on admission and reflected the general ill health. A loss of 50 pounds in one patient and 20 in another was recorded.

*Skin lesions.*—It is not the purpose of this paper to discuss or to classify our cases according to their dermatological types. We subscribe to the belief held by many others that the cutaneous lesions are merely the local manifestation of a systemic disease. However, at this point it should be recognized that in certain cases of chronic discoid lupus dissemination may occur, accompanied by the other signs of a generalized process.

A rash typical of disseminated lupus erythematosus was present in all of our patients at some time. It was the earliest sign in only 3 cases; it coincided with other symptoms in 2, and was preceded by other symptoms (usually joint pains) in 6 cases. A marked stomatitis, with superficial ulceration, was observed in 3 patients, and in one it appeared before the erythematous rash. In one case the skin lesions were apparently precipitated by the use of gold therapy in the belief that the patient had rheumatoid arthritis.

*Joint manifestations.*—Pain, swelling, tenderness and increased temperature without redness are the characteristic joint changes found in this disease.[5] The arthritis often precedes

* Read before the British Columbia Society of Internal Medicine, February, 1948.

the cutaneous lesions. The degree of joint involvement varies considerably. The early clinical picture may resemble, and may be confused with both rheumatoid arthritis and rheumatic fever. Unlike the former, however, permanent and progressive pathological changes are unusual, and unlike the latter this arthritis responds poorly to treatment. Both the larger and smaller joints may be involved. Fibrositis or periarthritis, rather than arthritis, may dominate the picture. A long-standing history of recurring muscular aches and pains with associated stiffness is not unusual.

It is interesting to note that 10 of our 11 patients had prominent joint symptoms. Arthritis or fibrositis was a presenting complaint in 9 cases, and preceded the onset of the skin rash in 4. The hands and feet were most often affected. However, pain in the elbows, shoulders, knees and ankles was not uncommon. The principal joint symptom was pain with some limitation of movement. In a few cases tenderness and swelling were demonstrated. Redness was infrequent. An early diagnosis of acute rheumatic fever was made in 5 cases and of rheumatoid arthritis in 2. In the remaining 3 patients the joints were not acutely involved, the arthralgia being of gradual onset. The persistence of pain in the muscles and joints after the acute phase had subsided was characteristic. Numbness of the arms and shoulders was a prominent symptom in three individuals.

*Blood and blood-forming organs.*—In most cases there is evidence of decreased bone marrow activity, with uniform depression of red and white blood cells and thrombocytes. The anæmia varies in degree and in our group 8 cases had a moderate to marked normochromic anæmia. Supportive therapy (transfusions and iron) was ineffective. One patient had a severe hypochromic anæmia. In this instance, however, bleeding from the gastro-intestinal tract was a pronounced feature. Recently, a distinctive cell, possibly a mature polymorphonuclear leucocyte containing inclusion bodies, was described in the bone marrow of patients with disseminated lupus erythematosus.[6] A search for this so-called L-E cell in one of our cases was fruitless. The bone marrow was hypoplastic in one subject, and normal in the 2 others examined.

Leucopenia with uniform reduction of all white blood cells in the circulating blood is a feature of this disease. However, in a group of 65 cases from the Massachusetts General Hospital only 30% are reported to have had a leucopenia.[7] Leucocytosis may occur in the presence of superimposed infection. In our series leucopenia was marked (*i.e.*, below 3,000 cells per c.mm.) in 6 cases; the other 5 had at least one or more counts within the range of 3,000 to 5,000. The general range was 3,000 to 7,000. In response to intercurrent infection polymorphonuclear leucocytosis occurred in 2 cases. In three other patients the leucopenia persisted but there was a relative increase in neutrophiles and staff cells. In 4 cases 1 to 2% plasma cells were noted in the circulating blood.

The sedimentation rate is elevated and remains so throughout the course of the disease—a finding constantly observed in our group. The total serum protein is usually within normal range. In a review of 30 patients by Coburn and Moore,[3] inversion of the albumin-globulin ratio occurred in all cases investigated. They believed that this increase in gamma globulin was typical of the disease. Although it did not precede the clinical onset it was constantly present and reflected the activity of the disease, globulin increasing during exacerbations and decreasing during the remissions. In only one of our patients was this reversal of the albumin-globulin ratio noted. One case had a normal total protein level with a normal albumin-globulin ratio. In the other three cases tested total proteins were either normal or low, and the A/G ratios were not obtained.

Coburn and Moore[3] reported positive Kline tests in 13 of 30 cases tested, and a positive or anti-complementary Wassermann reaction in 11 cases. This false serological reaction may be caused by some change in the character of the gamma globulins in disseminated lupus erythematosus. In one patient reported by Keil[8] a paretic type of colloidal gold curve was obtained in the cerebrospinal fluid. Two of our subjects had false positive serological tests for syphilis. In one case, with the onset of acute arthritis several years before the final admission, the Kahn was positive. Later it reverted to normal with remission of other symptoms. On the final admission it was again positive to 20 units and later dropped to 4 units. The cerebrospinal fluid

Kahn was negative but she had a paretic type of colloidal gold curve. The second case had a negative blood Wassermann reaction with a positive Kahn, which later was reported as doubtful.

Low serum calcium and vitamin C levels have been reported,[3] but these were not determined in our study. Repeated blood cultures were uniformly negative in all 11 patients.

*Kidney involvement.* — Abnormalities of the urine are present in most instances. They are non-specific, and like the cutaneous lesions, may be temporarily reversible. The most constant finding is albuminuria which varies in its severity from 1 to 4 plus. Casts and red blood cells occur later but are not as frequent as the albuminuria. The persistence of these urinary changes with little evidence of progression over long periods suggests that they are a relatively mild reaction to some toxic process.[9]

In our study, albuminuria was observed at some time in all except one case. The level was usually low, from 1 to 2 plus. White blood cells were found in small numbers in 8 cases, and the occasional red blood cell in 6. Frank hæmaturia was noted in one patient. Casts were only rarely observed. The concentrating power of the kidneys was good and renal azotæmia with terminal uræmia did not occur.

*Genital tract.*—Menstrual irregularities including amenorrhœa, menorrhagia and metrorrhagia were noted in five patients.

*Lymphatic system.*—Lymphadenopathy is generally considered to be common. However, clinical evidence of glandular enlargement in several series was present in only one-third of cases.[3, 4, 10, 11] The glands are usually few in number and are found in the common gland areas in different combinations, or occasionally in one area alone. In our study, 6 patients had lymphadenopathy demonstrable clinically, and in one additional case enlargement of the paratracheal glands was seen by x-ray. In several instances the glands were described as being moderately enlarged, firm, non-tender, freely movable and non-adherent. Clinical enlargement of the spleen is unusual. This is confirmed by observations in our group, in which this organ was not recorded as being palpably enlarged in any of our series.

*Serositis.*—Involvement of the serosal membranes,[3, 4] as evidenced clinically by pleural, substernal and abdominal pain, friction rub and effusion, is relatively common. This is confirmed by x-ray and electrocardiographic changes. Six of our 11 cases had pleural involvement—that is, they had one or more of the following signs—pleural pain, pleural effusion, friction rub or changes in the chest film. In two patients pleurisy preceded the other symptoms, and was a presenting complaint on admission to hospital. In three additional patients pleural effusion was found at autopsy.

Pericardial effusion was seen in 4 cases. These were all diagnosed clinically. A friction rub was heard in one; severe precordial pain was present in another. Three patients had enlargement of the cardiac shadow, suggesting effusion. Electrocardiographic changes in keeping with this diagnosis were present in two cases. Involvement of the peritoneum frequently occurred. Abdominal pain (mainly upper abdominal) was a presenting symptom in 3, and occurred at some time in 7 patients. It was very persistent in two instances. Diffuse abdominal tenderness was demonstrated in 3 subjects.

*Cardiovascular system.*—The clinical features in regard to the cardiovascular system are neither constant nor characteristic of the disease. The heart rate is rapid, reflecting the height of the fever. There is no constant alteration in the blood pressure. The electrocardiograms may be abnormal. Low voltage, reflecting damage to the myocardium, is the most common finding. Death is not usually due to myocardial failure *per se*. This was borne out in our study. The pulse rate followed the temperature elevation. Hypotension occurred in 2 patients. Electrocardiograms were obtained in 5 cases, 2 of which were within normal limits. Definite myocardial involvement was present in the other 3. In no patient was a changing murmur recorded. Systolic murmurs, however, were noted in 4 cases. Cyanosis was marked in one subject and gallop rhythm in another.

*Central nervous system.*—Signs and symptoms of central nervous system involvement[10, 12] are variable. Confusion, depression, irritability, chorea, etc., are described. However, some patients show no such changes and remain lucid to the end. In our review some mental disturbance was noticed in 9 patients. Early in the course of the final admission the symptoms of irritability, sleeplessness, excitability and emo-

tionalism were more common, with clouding of the sensorium, confusion, depression, stupor and delirium occurring terminally. One patient had a grand mal attack shortly before death. One patient was reported to have had a "nervous breakdown" with the onset of the disease 2 years before death. Marked loss of memory was a feature of one case. Chorea was not reported in any of our group.

*Ocular manifestations.*—Maumanee[13] reported three lesions in the retina which may be found in typical cases. The first of these were small, fluffy white or yellow white exudates in the superficial layers of the retina. They were never larger than the disc and were similar to those found in hypertensive retinopathy. The second were small superficial retinal hæmorrhages. Slight papillœdema completed the triad. Wagener[14] agrees that these changes are due to the generalized toxæmia. Bilateral optic atrophy with narrowing of the retinal vessels and atrophic changes in the retina have also been described in this disease.[14] In our series no record of the above retinal lesions was found.

## POST-MORTEM FINDINGS

Five of our 11 cases were examined at autopsy. The findings at post-mortem in clinically proved cases of disseminated lupus erythematosus may be quite disappointing. Klemperer, Pollack, and Baehr,[11] in a complete analysis of 20 cases in 1941 evolved a group of pathological criteria which is both simple and comprehensive.

The fundamental pathological process takes place in the connective tissue where injury to all the elements of that tissue occurs—cells, fibres and ground substance. This alteration, which may affect connective tissue anywhere in the body, they term a fibrinoid degeneration. The variability in both degree and extent of the process accounts for the diverse manifestations of the disease.

The vascular changes are similar no matter where found. There is fibrinoid degeneration in the subendothelial layers of the intima, with secondary changes occurring in the covering endothelium, frequently leading to thrombosis. The other connective tissue elements of the vessel wall may take part in the process, resulting in its destruction. The heart is frequently enlarged. Endocardial vegetations, described by Libman and Sacks[15] as a separate entity under the title of "Atypical Verrucous Endocarditis", are now thought to be a local variant of this disease. Fibrinoid degeneration affects the valvular and mural endocardium, the endocardial layer being finally destroyed with the formation of small vegetations. Libman-Sacks endocarditis was encountered in one of our cases. It involved the mitral valve and did not extend on to the mural endocardium. Early thickening and degeneration of collagen fibres beneath the endocardium was seen in another case.

Grossly, all hearts were soft and flabby and on microscopic examination 2 cases showed perivascular fibrosis with necrosis and mononuclear cell infiltration. Involvement of the serosal membranes is very common. Pericardial effusion was present in 4 cases. A thick, white, shaggy, fibrinous exudate was encountered in one of these. Three cases had a clear, straw-coloured, pleural effusion and bilateral empyema was found in a fourth. Although abdominal pain was a common symptom, peritoneal effusion was only found in 2 cases and one of these had had no abdominal complaints.

Two microscopic findings in the kidney are thought to be characteristic of this disease. Fibrinoid degeneration in the basement membrane of the glomerular tuft gives it the so-called "wire-loop" appearance. Two of our cases displayed this picture. The second change which is described is focal necrosis of the glomerular loop, and this was present in a third case. The kidney may show little evidence of pre-existing disease, a fact which was borne out by the absence of more than minimal changes in two cases.

The lymph nodes microscopically show œdema with engorgement and irregular areas of necrosis. Three of our cases were in the group. Although there was clinical enlargement of the lymph glands in a fourth case, no abnormalities were seen at post-mortem examination. The spleen characteristically shows periarterial fibrosis. This condition was thought to be specific by Kemperer and his co-workers, who found it in 19 out of 20 cases. However, it has been shown to occur in other diseases. We found it in only one of our cases. Focal necrosis of the liver is described but is not a feature of our series, although fatty degeneration and fibrosis were present in 4 cases.

In the skin, one case showed a marked œdema of the corium and papillary bodies, fibroblastic proliferation and degeneration, infiltration with mononuclear cells and fibrinoid degeneration of the capillaries—findings which are in keeping with this disease.

No case showed evidence of active or healed tuberculosis.

Although a definite diagnosis of disseminated lupus erythematosus was made on clinical grounds in these 5 cases, typical changes were present in only three and in the remaining two, the findings were not inconsistent with the diagnosis.

*Etiology.*—The etiology of disseminated lupus erythematosus remains obscure.[16 to 19] Various theories appear in the literature linking this condition with others having similar pathological changes. To date however, there is little upon which a sound hypothesis can be based.

*Treatment.*—No treatment has yet been found to be of value. Prophylactically, direct exposure to sunlight and the injection of allergenic substances such as tuberculin are to be avoided. Gold therapy is contra-indicated. Once the disease is established therapy is purely symptomatic.

### DIAGNOSIS AND DISCUSSION

The diagnosis of disseminated lupus erythematous may be extremely difficult especially before skin lesions are present. This difficulty is due to the various clinical findings and to the fact that until now no single laboratory test which could confirm a suspicion of the disease has been available. The diagnosis has to a large extent been one of exclusion. The comparatively slow progress of the disease has often delayed final classification. We do not intend to discuss the differential diagnosis of the skin lesions but it is obvious that when a chronic lupus erythematosus has been previously present, dissemination of the process will be more readily recognized. The same applies in those cases where skin lesions appear concurrently or soon after the development of general symptoms.

Joint pains are likely to be confused with rheumatic fever or rheumatoid arthritis. The fact that salicylates often relieve the pain temporarily will add to this confusion with rheumatic fever early in the course of the disease. The pain will recur, and this, together with the fever and elevated sedimentation rate often suggests rheumatoid arthritis. It may be extremely difficult, or impossible for a time, to exclude this diagnosis. In lupus, however, it is quite unusual to find permanent joint changes, which is an important observation. Furthermore, there may be the associated manifestations (enlarged lymph nodes, changes in the ocular fundi, and urinary abnormalities) which are not seen in rheumatoid arthritis. Another point which has struck us in this regard is that the joint symptoms vary from day to day and week to week—much more so than in rheumatoid arthritis. This differentiation is important, not only from the point of view of accurate diagnosis and prognosis, but also because gold therapy may be definitely harmful in disseminated lupus.

Patients presenting with a fever of unknown origin and leucopenia immediately bring many conditions into the differential diagnosis. These include tuberculosis, the typhoid group, and undulant fever. X-ray and laboratory examinations will exclude these. Subacute bacterial endocarditis will be considered. Blood cultures are sterile in disseminated lupus, and clinically important new valvular lesions are unlikely to develop. Secondary syphilis may have to be excluded where generalized lymphadenopathy is associated with fever and a skin rash. A positive blood Kahn adds to the difficulties. Differentiation will be based on the lack of exposure or primary lesion, and the low titre of the blood Kahn. Furthermore, the Kahn may become negative spontaneously at any time. Darkfield examination of material from the skin lesions will be negative.

The urinary findings have to be differentiated from those of glomerulonephritis. This may be difficult, but azotæmia of important degree does not develop in lupus. Pericarditis is not usually an early feature. Pleurisy may occur early; its true nature will be determined when other causes have been excluded and by its association with the other protean manifestations of this disease. These, however, may not appear until some time later. The diagnosis of the lymphadenopathy also depends on the exclusion of other causes and its correlation with additional findings in the entity under discussion.

Finally, it has seemed to us worthwhile to complete this paper with a typical case history.

Although there are a great many variations in the clinical picture of the disease, nevertheless, there is a fairly common pattern which should suggest the correct diagnosis.

The patient is a young woman who may or may not have a skin lesion, particularly of the face. This skin lesion may recently have spread following exposure to sunlight. She gives a history of having had variable joint pains of months', or a few years' duration. She has almost certainly been told that she had rheumatic fever or rheumatoid arthritis, or both. She may recently have received gold therapy for these joint symptoms. Her other complaints are those of chronic ill-health. which her appearance may belie. Fever may have been observed. Pleuritic pain may be the presenting complaint. Examination frequently is disappointing and reveals few or no significant abnormalities. However, there may be enlarged lymph nodes, signs of pleurisy, fever, and lesions of the skin and buccal mucous membranes.

The joints are likely to be normal on both clinical and radiological examination. A leucopenia is present, the sedimentation rate is elevated and a normochromic or hypochromic anæmia is found. This anæmia will be refractory to any treatment except transfusions. Serological test for syphilis may be positive in a low titre, perhaps only temporarily. All laboratory investigations commonly used in fever of unknown origin are negative. Under symptomatic therapy the patient may improve, even to the extent of having a few months or more of comparatively good health. On the other hand, the progression of the disease may be slowly or rapidly downhill until death occurs.

In the late stages, pyrexia of some degree will certainly be present. Pleurisy and pericarditis may become manifest. By this time too, very widespread visceral involvement is quite evident. The sensorium may remain clear to the end, or stupor, delirium and unconsciousness may supervene.


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RÉSUMÉ

Les lésions profondes du lupus érythémateux diffus placent cette maladie dans la province du médecin général plutôt que dans celle du dermatologiste. L'éruption cutanée apparaît, d'une façon caractéristique, sur les parties découvertes, et s'aggrave par l'exposition aux rayons solaires. Cependant, au début de la maladie, elle fait souvent défaut; par contre, les douleurs articulaires, avec gonflement et limitation des mouvements, se trouvent dans la plupart des cas parmi les premiers symptômes. On rencontre aussi, très souvent, des épanchements dans les plèvres et le péricarde, une albuminurie à laquelle correspondent des lésions glomérulaires typiques, une adénopathie lymphatique, des souffles cardiaques en rapport avec une endocardite végétante. La maladie frappe ordinairement les femmes dans la vingtaine. Elle évolue avec fièvre, anémie, leucopénie et hypersédimentation globulaire, vers la cachexie progressive et la mort, au bout de 20 mois en moyenne chez les malades qui font l'objet de cette communication. PAUL DE BELLEFEUILLE


# VASCULARIZATION OF THE MYOCARDIAL CAPILLARY BED BY ARTERIALIZATION OF THE CARDIAC VEINS: AN EXPERIMENTAL STUDY*


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THE purpose of these experiments is to determine if the myocardial capillary bed can be perfused with arterial blood directed through the cardiac veins. The practical purpose is the re-establishment of adequate myocardial circulation in human cardiac ischæmia due to coronary arterial sclerosis. These experiments were commenced in June, 1946. Since then 356 operations have been done on 240 dogs.

*Can the myocardial capillary bed be reached through the veins?*—There are no valves in the coronary sinus tributaries. The vestigial valve at the left end of the coronary sinus is incompetent and usually offers no obstruction to retrograde flow.

Perfusion experiments on the dead heart indicate that the perfusant is shunted from the veins to the heart cavities by-passing the capillaries.[1] Perfusion of the contracting heart, however, indicates an adequate venous-capillary connection. Roberts, Browne and Roberts[2] created an arterio-venous fistula between a systemic artery and the coronary sinus by means of a glass connection. Injection of dye indicated adequate capillary perfusion. The filling of the capillaries through the cardiac veins in the beating heart has been established by means of injection into the right auricle. The venous and arterial trunks arising from the heart are occluded as the injection is made. The capillary system is injected by the auricu-

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lar route, the coronary sinus and the cardiac veins.[3] Beck and co-workers,[4] by immediate injection of heparinized blood into the coronary sinus of the excised heart, gained the impression that there is no wide-open fistula effect either within the myocardium or in the superficial veins draining blood directly into the right atrium.

ink are injected. The entire left ventricle and a portion of the right ventricle turn black. Histologic sections show the ink throughout the capillaries.[6] It was not determined how much of the ink traversed the capillaries and how much was diverted directly to the heart lumen via luminal (Thebesian) or superficial venous (anterior cardiac) channels. The gross

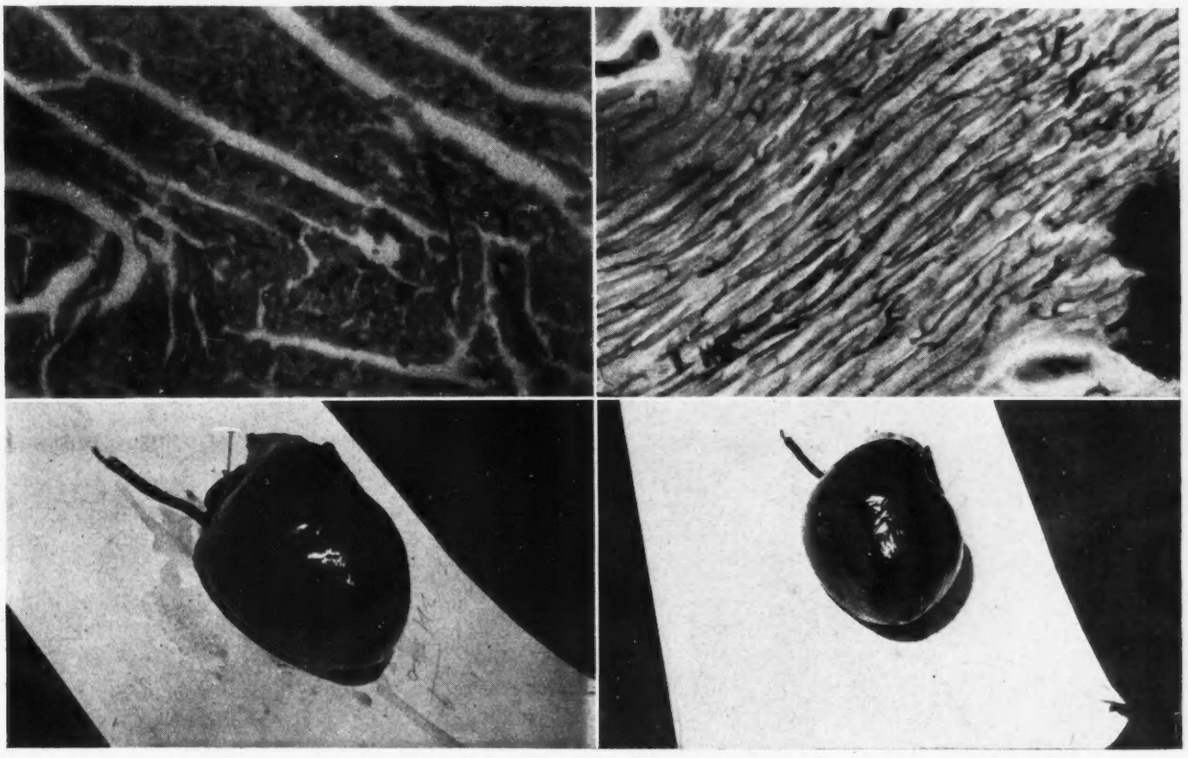

**Fig. 1.**—(A) Cross-section left ventricle showing India ink in the capillaries. (B) Longitudinal section left ventricle showing India ink in the capillaries. **Fig. 2.**—(A) Right anterior view of heart showing ecchymosis of left ventricle. Carotid artery upper left entering coronary sinus. (B) Anterior view of heart showing ecchymosis of left ventricle extending just beyond inter-ventricular groove.

In a number of experiments the capillary bed has been perfused in the beating heart by retrograde injection of India ink. This has not been successful in the heart long dead. The procedure used is not comparable to the living heart *in situ* and is open to criticism. It is, however, an indication that the capillaries may be reached through the veins. The coronary sinus is completely occluded at its termination[5] and a cannula inserted. The heart is then excised and whilst still contracting 20 c.c. of

and microscopic appearance of the ventricle suggest that the capillaries are adequately perfused[6] (Fig. 1).

*The systemic artery-cardiac vein anastomosis.*—There are a number of possible ways in which arterial blood can be delivered to the coronary sinus. Many dogs have been employed in an endeavour to determine the easiest and most satisfactory method to accomplish this. The procedures which have been done are as follows:

| *Artery* | *Cardiac vein* | *Anastomosis* |
|---|---|---|
| Left internal mammary | Great cardiac | End-to-end tube |
| " and right internal mammary | Coronary sinus | End-to-side tube and suture |
| " subclavian | " " | End-to-side tube and suture |
| Aorta | " " | Side-to-side and side-to-end suture |
| Left auricle | Creat cardiac | End-to-end tube |
| " atrium | Coronary sinus | Fistula |
| " ventricle | " " | Fistula |
| " and right carotid | " " | End-to-end and end-to-side tube and suture |

The extensive cardiac manipulation necessary to effect these anastomoses is well tolerated and with few exceptions operative death occurs only from systemic artery or cardiac vein hæmorrhage.

*Arterialization of the cardiac veins.*—When the anastomosis is completed and the occluding clamps removed the coronary sinus becomes very tense and increases in size. Its colour changes from dark blue to pale purple. It pulsates in rhythm with the systemic artery. Aspiration of the sinus reveals red blood under high pressure. A systolic thrill is occasionally produced. The surface veins of the left ventricle become lighter in colour and sometimes actual pulsation can be seen although this is difficult to assess in the beating heart. No obvious change has been observed in the appearance or rhythm of the heart.

*Left ventricular ecchymosis.*—This is the first great obstacle. About one-third of the dogs that survive with a functioning anastomosis die within the first 48 postoperative hours. Autopsy reveals the constant finding of diffuse left ventricular ecchymosis. The right ventricle adjacent to the interventricular groove is similarly affected. The hæmorrhage extends for a short distance into the left ventricular muscle and completely through the involved part of the right ventricle (Fig. 2). Histologic sections show free blood in the subepicardial fat and occasionally rupture of large veins. The blood extends through the entire ventricular wall but is less toward the endocardial surface. The veins and capillaries are enlarged. It is not known definitely that the effect of this myocardial hæmorrhage is the cause of death but it is presumed to be so. Some animals survive 48 hours with a functioning anastomosis. It is not known whether their hearts pass through this stage of myocardial ecchymosis but there is some evidence to suggest that they do. Some dogs have died of infection one to two weeks after successful anastomosis. The stomas were patent. The hearts were enlarged but grossly did not show ecchymosis. Histologic sections of the ventricle show extensive areas of muscle cell degeneration which can easily be seen under the low power. Some cells are swollen not unlike bundle of His cells. Others have lost all striations and look like young connective tissue. The capillaries are generally enlarged with no change in the larger vessels.[6] This may be the result of the ecchymosis.

Hæmorrhage into the wall of the left ventricle after systemic artery-coronary sinus anastomosis has been noted by other investigators.[4, 7] It has been noted when death occurs within 48 hours after complete occlusion of the coronary sinus. Other investigators have reported likewise.[8, 9] Beck and coworkers[4] suggest that the inability of the cardiac veins to withstand the increased pressure of sinus ligation and arterialization is due to malnutrition. They report that in healthy dogs which are fed meat and liver this lesion does not occur.

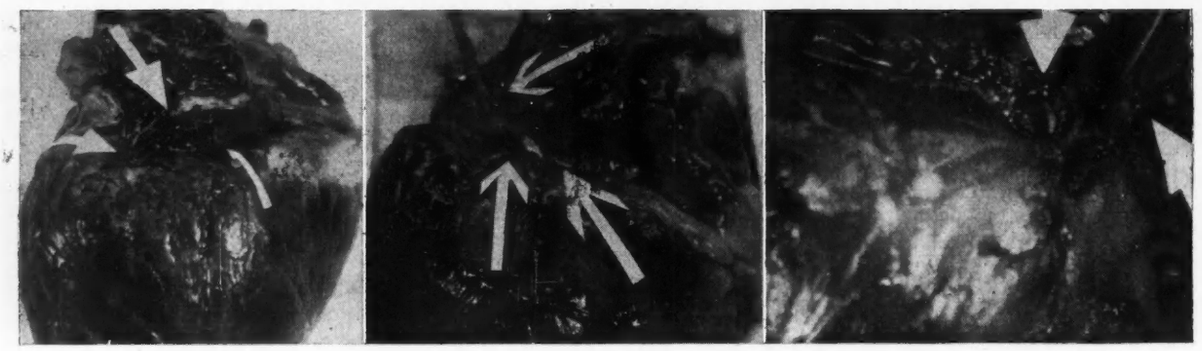

**Fig. 3.**—(A) The arrow on the right indicates the opening of the coronary sinus into the right atrium. Middle arrow—the end-to-side carotid artery—coronary sinus anastamosis. Left arrow—the entrance of the great cardiac vein into the coronary sinus. (B) The right lower arrow indicates the coronary sinus opening into the right atrium. Left lower arrow—the partial occlusion of the coronary sinus. Upper arrow—the end-to-side carotid artery—coronary sinus anastomosis. (C) The right arrow indicates the carotid artery. The left arrow—the end-to-end carotid artery—coronary sinus tube anastomosis.

*Anastomotic occlusion.*—This is the second great obstacle. The majority of dogs that survive the operation are eventually found to have complete or partial occlusion of the anastomotic stoma by a thrombus in various stages of organization. The frequency of this

complication can probably be reduced by the employment of perfect technique, a-traumatic occluding clamps, application of the high-low pressure principle, and heparinization.

*The operation.*—As indicated previously a number of procedures have been done in order to find the easiest and at the same time the most satisfactory method to effect arterialization of the coronary sinus (Fig. 3). The procedure which has been fairly satisfactory is as follows. The right common carotid artery is divided at its bifurcation and pushed into the thorax. The termination of the coronary sinus is dissected out of the heart wall and an end-to-side everting suture anastomosis is affected. The coronary sinus is left open into the right atrium. One week later the termination of the sinus is doubly ligated and divided. It is felt that a high-low pressure across the anastomosis for a week may help to keep the stoma open. Recently, because of the frequency of left ventricular ecchymosis, preliminary temporary occlusion of the sinus ostium has been done one week prior to anastomosis. Two weeks after anastomosis the anterior descending branch of the left coronary artery is divided at its origin.

*Criterion of myocardial vascularization.*—Gross and co-workers[10] state that occlusion of the anterior descending branch of the left coronary artery just beyond its origin causes ventricular fibrillation in about 50% of dogs. In the other 50% an infarct is produced which almost invariably measures 5 x 5 cm. on the surface. Personal experience with ligation of this artery at its origin suggests that 50% immediate death by fibrillation is too low. It is in the neighborhood of 75%. If survival occurs an infarct is produced in the left ventricular wall which is constant in size and position. Prevention of ventricular fibrillation and prevention or reduction in size of the infarct are used to indicate myocardial revascularization.

## RESULTS

TABLE I—ACUTE EXPERIMENTS

| *Number of dogs* | *Type of operation* | *Operative death* | *Death by ligation anterior descending branch left coronary artery* | *Death by ligation entire left coronary artery* |
|---|---|---|---|---|
| 10 | Internal mammary—coronary sinus (tube) | 2 | 5 | 2 |
| 8 | Aorta—coronary sinus (suture) | 6 | 0 | 2 |
| 7 | Left internal mammary—great cardiac vein (tube) | 4 | 0 | 3 |
| 5 | Left auricle—great cardiac vein (tube) | 4 | 1 | 0 |
| 5 | Left atrium—coronary sinus (fistula) | 1 | 4 | 0 |
| 5 | Left ventricle—coronary sinus (fistula) | 4 | 0 | 1 |
| 5 | Left subclavian artery—coronary sinus (tube) | 1 | 3 | 1 |
| 5 | Right common carotid artery—coronary sinus (tube) | 2 | 1 | 2 |

TABLE II.

ARTERIOVENOUS ANASTOMOSIS WITH COMPLETE SINUS OCCLUSION. IMMEDIATE LIGATION OF ANTERIOR DESCENDING BRANCH OF LEFT CORONARY ARTERY.

| *Number of dogs* | *Operative death* | *Death from fibrillation* | *Anastomosis* | *Death with ecchymosis* | *Anastomosis* | *Death from infection or distemper after 48 hours* | *Anastomosis* |
|---|---|---|---|---|---|---|---|
| 67 | 6 | 20 | 12 patent<br>7 partially occluded<br>1 occluded | 15 | 10 patent<br>4 partially occluded<br>1 occluded | 3 | 0 patent<br>0 partially occluded<br>3 occluded |

| *Number of dogs surviving 48 hours* | *Typical infarct* | *Anastomosis* | *Reduced infarct* | *Anastomosis* | *No infarct* | *Anastomosis* |
|---|---|---|---|---|---|---|
| 41 | 32 | 2 patent<br>5 partially occluded<br>25 occluded | 3 | 0 patent<br>3 partially occluded<br>0 occluded | 6 | 2 patent<br>4 partially occluded<br>0 occluded |

TABLE III.

ARTERIOVENOUS ANASTOMOSIS WITH INCOMPLETE SINUS OCCLUSION. IMMEDIATE LIGATION OF ANTERIOR DESCENDING BRANCH OF LEFT CORONARY ARTERY

| *Number of dogs* | *Operative death* | *Death from fibrillation* | *Anastomosis* | *Death with ecchymosis* | *Anastomosis* | *Death from infection or distemper after 48 hours* | *Anastomosis* |
|---|---|---|---|---|---|---|---|
| 38 | 5 | 13 | 8 patent<br>5 partially occluded<br>0 occluded | 5 | 4 patent<br>0 partially occluded<br>1 occluded | 2 | 0 patent<br>1 partially occluded<br>1 occluded |

| *Number of dogs surviving 48 hours* | *Typical infarct* | *Anastomosis* | *Reduced infarct* | *Anastomosis* | *No infarct* | *Anastomosis* |
|---|---|---|---|---|---|---|
| 23 | 14 | 0 patent<br>0 partially occluded<br>14 occluded | 6 | 2 patent<br>4 partially occluded<br>0 occluded | 3 | 2 patent<br>1 partially occluded<br>0 occluded |

TABLE IV.

ARTERIOVENOUS ANASTOMOSIS WITH COMPLETE SINUS OCCLUSION. LIGATION ANTERIOR DESCENDING BRANCH LEFT CORONARY ARTERY TWO TO THREE WEEKS LATER.

| *Number of dogs* | *Operative death* | *Death with ecchymosis* | *Anastomosis* |
|---|---|---|---|
| 21 | 3 | 9 | 4 patent<br>5 partially occluded<br>0 occluded |

| *Number of dogs surviving 48 hours* | *Death from infection or distemper* | *Anastomosis* | *Death from fibrillation* | *Anastomosis* |
|---|---|---|---|---|
| 9 | 1 | 1 patent | 3 | 3 occluded |

| *Number of dogs surviving ligation coronary artery* | *Typical infarct* | *Anastomosis* | *Reduced infarct* | *Anastomosis* | *No infarct* | *Anastomosis* |
|---|---|---|---|---|---|---|
| 5 | 0 | | 2 | 2 partially occluded | 3 | 3 patent |

TABLE V.

ARTERIOVENOUS ANASTOMOSIS WITH INCOMPLETE SINUS OCCLUSION. LIGATION ANTERIOR DESCENDING BRANCH LEFT CORONARY ARTERY TWO TO THREE WEEKS LATER.

| *Number of dogs* | *Operative death* | *Death with ecchymosis* | *Anastomosis* |
|---|---|---|---|
| 64 | 23 | 6 | 3 patent<br>3 partially occluded<br>0 occluded |

| *Number of dogs surviving 48 hours* | *Death from infection or distemper* | *Anastomosis* | *Death from fibrillation* | *Anastomosis* |
|---|---|---|---|---|
| 35 | 10 | 1 patent<br>3 partially occluded<br>6 occluded | 11 | 0 patent<br>3 partially occluded<br>7 occluded |

| *Number of dogs surviving ligation coronary artery* | *Typical infarct* | *Anastomosis* | *Reduced infarct* | *Anastomosis* | *No infarct* | *Anastomosis* |
|---|---|---|---|---|---|---|
| 14 | 10 | 2 patent<br>0 partially occluded<br>8 occluded | 2 | 2 patent<br>0 partially occluded<br>0 occluded | 2 | 2 patent<br>0 partially occluded<br>0 occluded |

### INTERPRETATION OF RESULTS

*Ventricular fibrillation.*—The fibrillation rate from ligation of the anterior descending branch of the left coronary artery immediately after the completion of successful anastomosis is 35%. There is no marked difference between the rate with complete (31%) and incomplete (40%) sinus occlusion. The first 50 operations (Chart I) are not included as a record was not kept of the condition of the anastomosis. The rate from ligation two to three weeks after successful anastomosis with incomplete sinus occlusion is 12%. There was no instance of fibrillation in which the sinus was completely occluded.

*Left ventricular ecchymosis.*—The death rate from rupture of cardiac veins is 25%. With a functioning anastomosis plus complete occlusion of the sinus the rate is 34% and with incomplete sinus occlusion 16%.

*Anastomotic occlusion.*—The total number of patent anastomoses is 60. The number in dogs surviving over 48 hours and dying or being sacrificed within six weeks is 19. The total number of partially occluded but probably or possibly functional anastomoses is 50. The number in dogs surviving over 48 hours is 25. The total number of occluded anastomoses is 70. The number in dogs surviving over 48 hours is 63.

*Infarction.*—Typical infarction occurred in 9 dogs despite functioning anastomoses. In all dogs in which the anastomosis was occluded typical infarction was present. Nine dogs survived without infarction following coronary artery ligation immediately after successful anastomosis. Another 9 survived with a reduced infarct. Five dogs survived successful anastomosis and delayed coronary artery ligation without infarction. In another four a reduced infarct was present. The number of functioning (patent or partially occluded) anastomoses at the time of sacrifice was 44. The number of hearts in which infarction was absent or reduced was 27.

### COMMENT

These experiments suggest that arterial blood can be delivered through the cardiac veins to the myocardial capillary bed and from the capillary bed to the heart lumen. The route traversed, however, is not known definitely. Gregg and Shipley[11] have questioned the Thebesian concept (Fig. 4) and have suggested that the superficial veins (Fig. 5) of the heart appear to play the dominant rôle in draining the coronary vascular bed. The anastomoses between the anterior cardiac veins and those contributing to the coronary sinus are extensive. When either superficial coronary venous system is acutely blocked the venous blood presumably passes into the right auricle by way of collateral communications to other unblocked venous channels. Gregg and Shipley emphasize the functioning of the superficial cardiac veins and tend to minimize

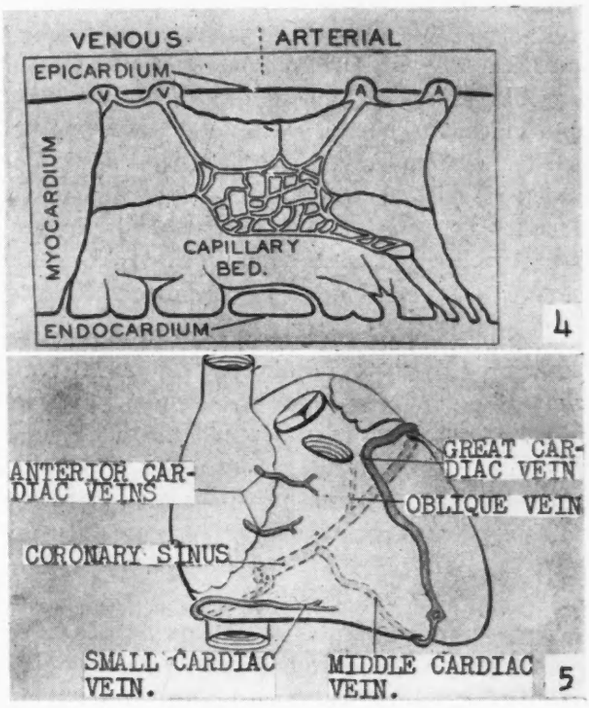


**Fig. 4.**—Thebesian vessels connecting arteries, veins and capillaries with heart lumen. **Fig. 5.**—Showing the alternate route (anterior cardiac veins) of venous return.

any rôle which the Thebesians may play in coronary drainage. On the other hand Roberts, Spencer and Browne[12] experimenting on 38 dogs have found that the lumenal (Thebesian) vessels drain blood from the myocardium into the cavity of the left ventricle in the heart beating *in situ*. They did not demonstrate the phase or phases of the heart's cycle during which such flow occurs.

The dog's heart tolerates well the extensive maniuplation required to effect the anastomosis. All the procedures which have been done are difficult and time-consuming. Tube anastomosis is associated with a greater incidence

of thrombosis than is the suture method. Suture anastomosis is associated with more dissection and trauma which increases the incidence of thrombosis. End-to-end right common carotid to coronary sinus one week after sinus ligation, at the moment, seems to be the most satisfactory method.

The frequency and severity of left ventricular ecchymosis is a major obstacle if this procedure is to be applied to the human heart. It may be that the human cardiac veins can tolerate sudden arterial pressure better than can the dogs. Preliminary partial or complete sinus occlusion may prepare the cardiac veins for blood under arterial pressure. End-to-side anastomosis with incomplete occlusion of the coronary sinus ostium reduces the incidence of ecchymosis. There is evidence to suggest that such a systemic artery-right atrium fistula is not serious.[13] Acute rupture of cardiac veins frequently causes death and evidence is presented which suggests that if survival occurs severe degeneration of heart muscle follows.

The prevention and reduction of infarction associated with a functioning stoma sugests that the area deprived of coronary arterial blood is supplied with arterial blood through the veins. However, the infarcts which occurred despite functioning anastomoses are not so easily explained.

SUMMARY

Three hundred and fifty-six operations have been done on 240 dogs. These operations consisted of anastomosis between a systemic artery and the coronary sinus plus coronary artery ligation. Arterial blood can be delivered to the myocardial capillary bed through the veins. Rupture of cardiac veins with resultant acute left ventricular hæmorrhage is a frequent cause of death. Occlusion of the anastomotic stoma by thrombosis is a frequent complication. The ventricular fibrillation death rate as a result of ligation of the anterior descending branch of the left coronary artery has been reduced by this procedure. Infarction has been prevented in 14 hearts and the infarct has been reduced in size in 13 hearts by the anastomosis.

Blalock and Johns[7] have done a number of similar anastomoses on dogs. Dr. Blalock has reviewed this paper and states that his results in general confirm the above.

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## ANURIA FOLLOWING ELECTROSHOCK THERAPY

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PRIOR to the war, little was taught about necrosis of renal tubules save that it occurred in cases of mercury and arsenic poisoning. During the Battle of Britain, the condition which came to be called crush syndrome[1 to 7] was recognized. The characteristic picture consisted of crushing of the limbs followed by the development of oliguria or anuria and uræmia. At autopsy, the findings were necrosis of skeletal muscle and large, pale kidneys with damage predominantly of the distal convoluted tubules.

Since these cases were reported, considerable interest has been shown in acute lesions of the renal tubules. A review of the literature has revealed that cases of fatal anuria following crushing injuries were described by German writers[8, 9] during, and after, the war of 1914-1918 and that Dunn and Polson,[10] in 1926, produced a focal necrosis, limited to the distal segments of the tubules, by the intravenous injection into rabbits of large doses of lithium monourate.

Following the recognition of crush syndrome with its characteristic renal lesions, there have been reports of numerous conditions which are typified clinically by anuria, which is frequently fatal, and pathologically by renal lesions which differ in no essential from those of crush syndrome. The group includes such widely divergent conditions as anuria following transfusion with incompatible blood,[11, 12] acute paralytic

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myohæmoglobinuria,[13] renal failure after sulfonamide therapy,[12] anuria due to heat stroke,[12] Weil's disease,[12, 14] anuria due to excessive vomiting,[15] and poisoning by carbon tetrachloride.[16] For a more comprehensive list of these conditions, the reader is referred to the paper of Maegraith, Havard, and Parsons.[17]

The purpose of this paper is to report a case, with a similar clinical and pathological picture, which terminated fatally after electroshock therapy. Although a case of fatal anuria following electric shock from a high tension wire has been reported by Fischer, Fröhlicher, and Rossier[18] and has been alluded to by Bywaters,[19] the writers have not encountered any report of anuria following electroshock therapy, nor do the Swiss workers include a description, either gross or microscopic, of the kidneys in their case. It is therefore felt that, in view of the widespread use of electroshock therapy in the treatment of psychiatric disorders, attention should be drawn to the possible occurrence of this serious complication.

## CASE REPORT

A white farmer, 59 years of age, was admitted to the Regina General Hospital on February 28, 1948, with a history of fleeting pains, insomnia, nervousness and sweating of the palms and the feet for several months, and of anorexia for two weeks. During the previous year or more, he had noted a loss of libido. His relatives had observed during the preceding few weeks that he had become increasingly agitated, with episodes of depression during which he had stated, "Nothing can be done to help me."

The only previous illnesses reported were pneumonia in 1939, with no sequelæ, and a transurethral resection of the prostate in 1947, with no subsequent urinary complaints except occasional burning on micturition. The patient's family history was non-contributory. His personal history indicated that he had always been of a tense, energetic, overly conscientious nature. The prostatectomy in 1947 and the fact that his wife had recently undergone a cholecystectomy were the only facts elicited which might be considered to have caused psychological trauma.

Examination showed the patient to be a tense, apprehensive, thin, white male, who appeared five years older than his stated age. The thyroid was not palpable. The chest was clear. The cardiac rhythm was regular, the rate 100 per minute, and no murmurs were audible. The blood pressure was 120/68. Although some of his pains were referred to the suprapubic region, there were no abnormal abdominal findings. Excepting a coarse tremor and hyperhidrosis of the palms and the soles, the findings on examination of the nervous system were within normal limits. The skin, except of the palms and the soles, was dry. With regard to his mental status, he was intelligent, obviously agitated, very introspective, and had poor insight. He had no delusions or hallucinations.

Urinalysis, on March 1, was negative chemically and microscopically, and the specific gravity was 1.015. The hæmoglobin content of the blood was 15.8 grams per 100 c.c., the sedimentation rate 4 mm. per hour, and the blood smear normal. The blood urea level was 25 mgm. %.

Electroshock therapy was carried out on March 1, 1948. With a dose of 110 volts and 450 milliamperes for 0.3 second, the patient had a typical grand mal convulsion with no immediate complications. The following morning, he stated that he had not passed any urine since the shock therapy and complained of aching in the lumbar region and nausea. Catheterization, on March 3, disclosed only one ounce of urine in the bladder. The intravenous administration of 5% glucose in distilled water was instituted; but, although the patient received 2,500 c.c. of this solution and 2 grams of aminophylline intravenously during the following twenty-four hours, his urinary output for this period was only one and a half ounces. The continued administration of glucose in distilled water and the application of hot packs thrice daily proved of no avail, as only one ounce of urine was found in the bladder on March 5, whereas the blood urea level was 123 mgm. %. The development of subcutaneous œdema, severe cough, and shortness of breath and the finding of dullness and râles at the base of the left lung dictated the discontinuance of intravenous fluids.

On March 6, bilateral ureteral catheterization and lavage of both renal pelves were carried out. On the same day, sympathetic block by high spinal anæsthesia was performed with the purpose of combating any arterial spasm in the kidneys, if such were present. These measures, however, failed to prevent the severe oliguria proceeding to anuria; only four ounces were voided that day and one and a half ounces on March 7. Catheterization later on March 7 was non-productive, and the patient died suddenly on March 8, almost seven days after the electroshock therapy, without having passed any more urine.

Urinalyses subsequent to the shock therapy showed from a trace to a heavy cloud of albumen, up to 10 white cells per high-power field, epithelial cells, amorphous phosphates and urates, and, in the last urine on March 7, frank blood. None of the specimens was darker than amber, except the last which contained blood. There is no record of casts having been found, and the urine was not specially examined for pigment.

## PATHOLOGICAL FINDINGS

(*a*) *Gross.*—Both pleural cavities contained fluid, whose volume could not be measured because of the fluidity of the blood and the copious bleeding that occurred while the chest was being opened. The volume was judged to be in the region of 200 c.c. in each pleural cavity. The left lung weighed 635 gm., the right lung 665 gm. The lower lobes were firm, non-crepitant, and dark purplish. Sanguineous fluid flowed from their cut surfaces. The two upper lobes and the middle lobe were moderately soft, crepitant, and pinkish-grey. Their cut surfaces were wet. The myocardium was flabby, but otherwise the heart was unremarkable. The aorta showed a moderate degree of atheroma. The abdominal cavity contained 125 c.c. of clear yellow fluid. The liver weighed 1,825 gm. and contained several small hæmangiomata. The spleen weighed 180 gm. and was very soft. There were numerous submucosal hæmorrhages of the urinary bladder. The brain weighed 1,265 gm. and showed nothing of note except minimal atheroma of the arteries at its base.

The most outstanding changes were in the kidneys. Both were enlarged, the right weighing 190 gm., the left 195 gm. Their capsules were stripped off easily, revealing pale surfaces on which the vessels stood out prominently. Sectioning showed the enlargement of the kidneys to be due to swelling of the cortex, which was wet and pale, contrasting with the medullary pyramids which were congested but judged to be of normal size. The mucosa lining the pelves and calices was œdematous and hæmorrhagic. There was a small subintimal hæmorrhage in the right renal artery. Otherwise the renal arteries appeared healthy.

(*b*) *Microscopic.*—In the pulmonary alveoli were hæmosiderin-laden macrophages, a few of which contained phagocytosed red cells. The spleen was markedly congested. Sections of the brain, pituitary, thyroid, liver, pancreas, and adrenals failed to show anything of note.

The renal lesions closely resembled those described in cases of crush syndrome. There was no evidence of previous disease, except slight muscular thickening of the arteries. The glomerular tufts were unremarkable. The superficial and deep glomeruli did not differ in the red cell content of their capillaries, although such a difference was particularly watched for. The epithelial cells of the parietal layer of Bowman's capsule of some of the glomeruli were more conspicuous and plumper than usual, and, near the outlet into the tubule, were cuboidal in form. The capsular space contained amorphous, eosinophilic debris. The proximal convoluted tubules were markedly dilated and contained the same type of amorphous debris as was noted in the capsular spaces of the glomeruli. There was no evidence of degeneration or of dedifferentiation of the epithelium of these tubules, its brush border being intact. The descending limbs of the loops of Henle showed nothing of note, save for the presence of the same type of debris as was seen more proximally.

In some of the ascending limbs of the loops of Henle, distal convoluted tubules, and collecting tubules, there was a brown, granular debris, which was benzidine-positive. The lumina of a few of the distal convoluted tubules contained degenerate epithelium either lying free or applied to the brown debris. Polymorphonuclear leukocytes were mixed with the debris in a small number of the tubules. The epithelium of many of the distal convoluted tubules showed regeneration, as evidenced by the flatness of the cells, their basophilic cytoplasm, and an occasional mitotic figure.

In addition to the brownish pigment, the ascending limbs, distal convoluted tubules, and collecting tubules contained ribbon-like, eosinophilic, hyaline casts. Some of the casts were partially calcified. A few completely calcified circular objects were bulging into tubules but were separated from the lumina by a layer of epithelium. These were interpreted as representing the previous extrusion, from damaged tubules into the interstitial tissue, of casts with subsequent regeneration of the tubular epithelium.

The venules of the cortex were unusually prominent, and about them there was evidence of recent disturbance. The interstitial tissue adjacent to these vessels was œdematous, was infiltrated by round cells and eosinophiles, and showed regimentation of proliferating fibroblasts. In some places, distal convoluted tubules bulged into the venules, while, in other places, the tissue containing fibroblasts bulged into the venule and separated it from a neighbouring tubule. The appearances were those of tubulovenous communications with almost complete healing.

The interstitial tissue of the cortex showed severe focal areas of œdema, with remnants of collapsed tubules, round cell infiltration, and fibroblastic proliferation. While the œdema was probably partially responsible for the swelling of the kidneys, the dilatation of the proximal convoluted tubules is considered to have been the major cause. The vessels of the medulla and, in some areas, even of the superficial portion of the cortex were congested. Hæmorrhagic areas were observed in the submucosa of the pelves and calices.

## DISCUSSION

Both the gross appearance of the kidneys, with their pale, swollen, wet cortex contrasting with the dark medulla, and the principal microscopic features, *viz.*, eosinophilic granular debris in the proximal portion of the nephron, damage of the epithelium of the distal convoluted tubules with desquamation and regeneration, pigmented and hyaline casts, tubulo-venous communications, infiltration of some cast-containing tubules by polymorphonuclears, and areas of œdema with fibroblastic proliferation, tallied with the de-

scriptions given of the kidneys in cases of crush syndrome and of the numerous other conditions mentioned above. Reference was made by Bywaters and Dible[1] to the fact that casts might be extruded into the interstitial tissue; and McLetchie,[15] in his case of excessive vomiting with anuria, found extrusion of casts into the interstitial tissue with calcification of the casts and regeneration of the epithelium. In the present case, a few examples of this were observed.

One of the outstanding features of the case under consideration was that healing was far advanced and that comparatively few of the distal convoluted tubules showed necrosis.

*Pathogenesis of anuria.*—Early in the study of crush syndrome, it was suggested (by analogy with the explanation given previously by Baker and Dodds[20] for anuria following transfusion with incompatible blood) that the anuria was due to blockage of the tubules by myohæmoglobin, which, having been released from the crushed muscles and readily passed by the glomeruli, was precipitated in the tubules, especially in an acid urine. Morison[5] believed that almost every tubule was obstructed at some level and that the epithelial changes were secondary. Bywaters and Beall,[4] on the other hand, pointed out that, if obstruction were the cause of anuria, the small volume of urine that *was* passed should be normal since it would be passed by unobstructed tubules. The fact, however, that the urine was found[2, 4] to contain a lower concentration of urea and a higher concentration of chloride than normal was indicative of tubular damage with impairment of selective reabsorption.

At the present time, there are two theories which attempt to account for the anuria. Bywaters[19] holds that precipitation, upon the epithelium of the distal convoluted tubules, of pigment derived from hæmoglobin (in the case of incompatible transfusions) or from myohæmoglobin (in the case of crushing injuries) inhibits absorption by these tubules, with the result that intrarenal pressure increases and causes dilatation and rupture of tubules, with the subsequent passage of the contents of the tubules into the interstitial tissue and thence into veins and lymphatics. On the basis of this theory, he would name the renal lesion pigment nephrosis.

Trueta and his associates,[21, 22, 23] on the other hand, as a result of their recent studies of renal circulation, believe that circulatory changes play an important part in the pathogenesis of the anuria in cases of crushing injury. In brief, these workers have shown that two courses are open to blood flowing through the kidney. The blood which passes through a glomerulus in the *peripheral* two-thirds of the cortex leaves the glomerulus by the efferent arteriole, passes through the intertubular capillary network in the cortex, and empties into an interlobular vein. On the other hand, the efferent arteriole issuing from a *deep* glomerulus, a so-called juxtamedullary glomerulus, divides into a number of vasa recta (vessels with the structure of capillaries, but of large calibre) which, after passing in a straight line down between the tubules of the medulla, loop upwards again to empty into interlobular veins. Blood following the latter course does not pass through the intertubular capillary network of the cortex.

These investigators demonstrated that by various experimental procedures the bloodflow through the superficial two-thirds of the cortex might be greatly reduced, with an increase in flow through the deep portion of the cortex and through the medulla. Among the methods found to produce such a change was obstruction, by means of a tourniquet, of the femoral artery of a rabbit. Of great significance was the observation that the obstructed artery and sometimes the contralateral femoral artery became spastic and that the spasm extended from the obstructed artery to involve also the iliac arteries, the infrarenal portion of the aorta, and the renal arteries. The explanation suggested for the decreased peripheral cortical bloodflow and the increased flow through the juxta-medullary portion of the cortex and through the medulla was that the injury to the limb caused reflex spasm of the peripheral portion of the interlobular arteries of the kidneys more readily than of the deep portion, so that, whereas the circulation through the juxta-medullary glomeruli was maintained, the amount of blood passing through the more peripheral glomeruli was sufficient only to prevent the occurrence of massive necrosis but was inadequate for the production of urine.

Trueta and his associates[23] are of the opinion that in cases of crush syndrome the anuria is largely due to renal cortical anoxia consequent upon reflex arterial spasm, but that other unknown factors probably also play a part. Maegraith *et al.*[17] have suggested that the many conditions which follow the same clinical

course and show the same pathological picture as crush syndrome should be grouped under the name of renal anoxia.

Bywaters,[19] while agreeing that intrarenal circulatory changes may occur, believes that such changes are not primary but are secondary to the sequence of events (precipitation of pigment, failure of absorption, and increase in intrarenal pressure) which has already been outlined.

If Bywaters' theory be correct, then the oliguria which occurred in the present case after electroshock therapy must be regarded as due to impairment of tubular absorption by the precipitation, on the tubular epithelium, of pigment derived presumably from muscle. It is unfortunate that the urine was not examined for such pigment and that the skeletal musculature was not carefully inspected at autopsy for areas of necrosis. The findings, however, by Fischer and his associates,[18] of myoglobin in the urine and of extensive necrosis of skeletal muscle in their patient who died two days after electric shock from a high tension wire give some support to the belief that the pigment in the tubules of the present case came from the muscles, although it must be remembered that the voltage and the amount of current passing through the two individuals differed greatly. The liberation of the pigment from muscle might have been due to damage of the muscle by the electric current either directly, or indirectly through vasospasm and a resultant ischæmia.

If, on the other hand, the oliguria was due to anoxia of the renal cortex, in accordance with Trueta's theory, then the suggested explanation is that the electroshock therapy caused spasm of the renal arterial tree, especially in the peripheral portion of the cortex, with a consequent shift of the renal bloodflow to the deep portion of the cortex and to the medulla.

It is impossible to say at present which of these mechanisms caused the oliguria or whether other unknown factors were responsible. It would seem that further studies of the renal circulation, of the effects of the derivatives of hæmoglobin and myohæmoglobin, and of the effects of electric shock are necessary in order to answer this question. It must be emphasized, however, that, in contrast with the almost complete anuria, the cytological damage was slight and healing was far advanced.

## TREATMENT

If spasm of the renal arterial tree be a factor in the causation of the anuria, then the interruption of sympathetic impulses to the kidneys, either by high spinal anæsthesia or by splanchnic block, would appear to be a logical form of therapy. There are reports of diuresis following high spinal anæsthesia in cases of Weil's disease with anuria[24, 25] and of recovery with splanchnic block following transfusion with incompatible blood.[26] Sufficient work has not been done, however, to establish the value of this treatment, as some cases[1] show a diuresis spontaneously. The present case, on the other hand, did not improve following spinal anæsthesia; and similar failures have been reported[27] in the literature.

The use of the artificial kidney[28 to 30] or of peritoneal dialysis[27, 31 to 33] would appear to be indicated in the treatment of these cases, inasmuch as structural damage of the kidneys is slight and the epithelial regeneration which is evident gives promise of a restoration of renal function if death can be averted during the period of anuria.

## SUMMARY

A case of fatal anuria following electroshock therapy has been described, and the close similarity of the renal lesions to those seen in crush syndrome and in a number of other conditions has been pointed out. The insignificance of the cytological changes, in contrast with the complete renal failure, has been emphasized.

The writers wish to express to Dr. N. G. B. McLetchie their gratitude for the assistance which he has so generously and willingly given in the preparation of this paper and to Dr. H. E. Baird, Superintendent of the Regina General Hospital, their appreciation for his permission to publish this case.

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## DIURETIC EFFECTS OF ŒSTROGENS IN THE LAST FOUR MONTHS OF PREGNANCY*

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THE problem of excessive weight gain during pregnancy concerns both the doctor and the patient; to the former it suggests an impending toxæmia, and to the latter it means wardrobe troubles, ungainliness, and strained arches causing painful feet. The expected gain of approximately twenty pounds[4, 13] in the course of a pregnancy usually taxes the patient's reresources in these three factors, and the greater the increase in bulk, the more inactive and sedentary the patient tends to become. This is particularly true of the patient who is overweight at the start of the pregnancy, and, in the interests of normal labour, strict limitation of further gain is indicated. The majority of women are anxious that their weight should remain within reasonable bounds, and are willing to co-operate with the medical attendant in the matter of diet or therapy.[8]

Because it is known that excessive weight gain is largely due to retention of fluids within the tissues, although true œdema may not be demonstrable, the usual therapeutic measure which is taken to produce an outpouring of fluid is the administration of magnesium sulphate to cause watery stools and a concomitant weight reduction. It is seldom taken into account that this iatrogenic diarrhœa may prevent the patient from going about her usual pursuits and amusements, and exaggerated intestinal motility may lead to a true dietary deficiency. Therefore it is desirable that diuresis in the pregnant woman should be brought about by less drastic and more physiological means.

It is the purpose of this paper to present a series of 40 cases of excessive weight gain in pregnancy, 77.5% of whom responded satisfactorily to the administration of small doses of œstrogens, suggesting that this hormone may be a useful adjunct to prenatal care. The weight changes observed in these patients are sufficiently marked to warrant further investigation of the problem on a scientific and endocrinological basis, as the findings are in disagreement with the generally accepted theory that œstrogens cause fluid retention.[1, 2, 4, 7, 9 to 11, 16]

In the matter of weight gain, pregnant women may be divided into three classes: first, those who go through the nine months with a steady average gain within normal limits; second, those who gain weight rapidly with overt œdema and later develop hypertension or albuminuria, making a pre-eclamptic picture; and third, those who gain excessively throughout the pregnancy despite restrictions in diet, and salt and fluid intake, yet develop no œdema nor other evidence of toxæmia. It is in this third class that the administration of œstrogens would appear to be useful in causing a diuresis resulting in slowing of the rate of gain, if not an actual reduction in weight, during the time that the hormone is being taken.

The patients in this study were those who began to gain rapidly in the early months of pregnancy, and who continued an excessive gain despite rigid limitation of carbohydrates, a maximum of eight cups of all kinds of fluid per day, and restriction of salt to a minimal use in cooking. If the weight gain continued above average on this regimen they were put on a daily dose of œstrogenic substance. In the majority of cases the preparation used was 2 mgm. benzestrol, three were given œstrone sulphate 1.25 mgm., and three were given ethinyl œstradiol

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0.05 mgm.; similar results were obtained from all preparations.[12] The patients were instructed to take the tablet at bedtime. Each patient's appointment was given at the same time of day for each visit to avoid diurnal weight fluctuations. The dietary restrictions were maintained, and the purpose of the medication was not revealed to the patient. Invariably on the next visit the patients would make an unsolicited complaint of increased bladder activity since taking the pills. Some of the patients connected the periodic reduction in weight gain with the tablets, and requested them at future visits.

It is obvious that data based on interval weighings in an office can claim no scientific accuracy. Also it is impracticable to expect the ambulant ordinary patient to measure urinary output with any assiduity over a prolonged space of time. However, one scientific-minded patient in the group volunteered to keep an accurate record of urinary excretion, and did so for fifteen weeks as shown in Fig. 2. Another patient undertook the bothersome chore, but lapsed at intervals (Fig. 3). The amounts of urine excreted each day are no doubt influenced towards the end of pregnancy by changes of pressure exerted by the fetal head in the pelvic cavity with possible retention of some urine for undetermined periods of time, but this factor should not be operative before the thirty-seventh week. That the slowing of the rate of gain, or an actual loss of weight, is due to a diuresis caused by the invested œstrogens would appear to be confirmed by the urine measurements coupled with the patients' voluntary expressions of increased kidney function.

Forty-three cases were given œstrogenic substances in the course of this study. Three cases have been discarded because labour began before the patients again visited the office; that the hormone caused the initiation of labour in these cases is problematical but seems unlikely as a similar effect was not noted in 13 other patients who were taking it equally near term. The weeks during which the pa-

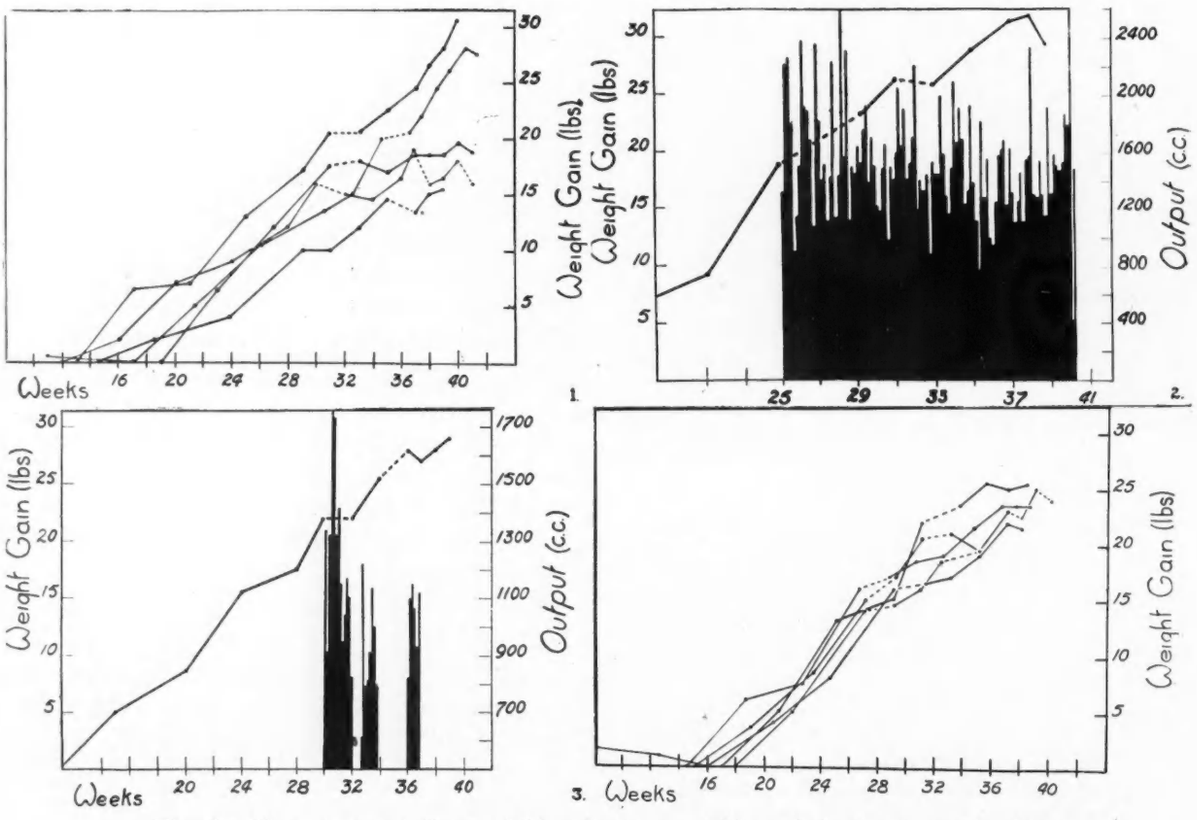


**Fig. 1.**—Five representative weight gain curves with period of œstrogenic therapy shown in broken lines. **Fig. 2.**—Daily urinary measurements plotted on weight gain curve showing increased excretion while on œstrogenic therapy (broken lines). **Fig. 3.**—Daily urinary measurements plotted on weight gain curve showing increased excretion while on œstrogenic therapy (broken lines). Also shows difficulty of obtaining a constant record of output from patient. **Fig. 4.**—Five curves of excessive weight gain showing weight limiting effect of œstrogenic therapy (broken lines); first course of treatment was given between 26 and 31 weeks.

tients were on the hormone are indicated by broken lines on the graphs, and the lessening of slant, plateau, or declivity of the weight gain curve is demonstrated in Figs. 1, and 4 to 6 inclusive. Three cases included developed symptoms of pre-eclampsia as the pregnancy progressed; two of these showed a limitation of weight gain on the œstrogens, but as the toxæmic symptoms developed later they were treated by the generally accepted methods rather than by pushing the sex steroids as is advocated by some investigators.[14, 15] Only two patients showed an added weight increment while on the œstrogens, and doubling the dose of the hormone was not effective in lessening the gain; one of these was brought under control with magnesium sulphate (Fig. 8). Another patient who gained excessively despite dietary control is shown in Fig. 8; she gained 36 pounds before the benzestrol was given, and added another two pounds thereafter. None of these extreme cases showed overt œdema nor other toxic signs, and all complained of frequency while taking the pills. In Fig. 7 are shown five cases who responded poorly to the therapy, with only a slight lessening of rate of gain. Excluding the group of patients which are represented in Fig. 7 and 8, there are 29 cases in which the response to œstrogenic therapy appears to be highly satisfactory. Over comparable periods of time, the difference in average gains is 2.33±0.27 pounds before taking the hormone, compared with 14 days of treatment.

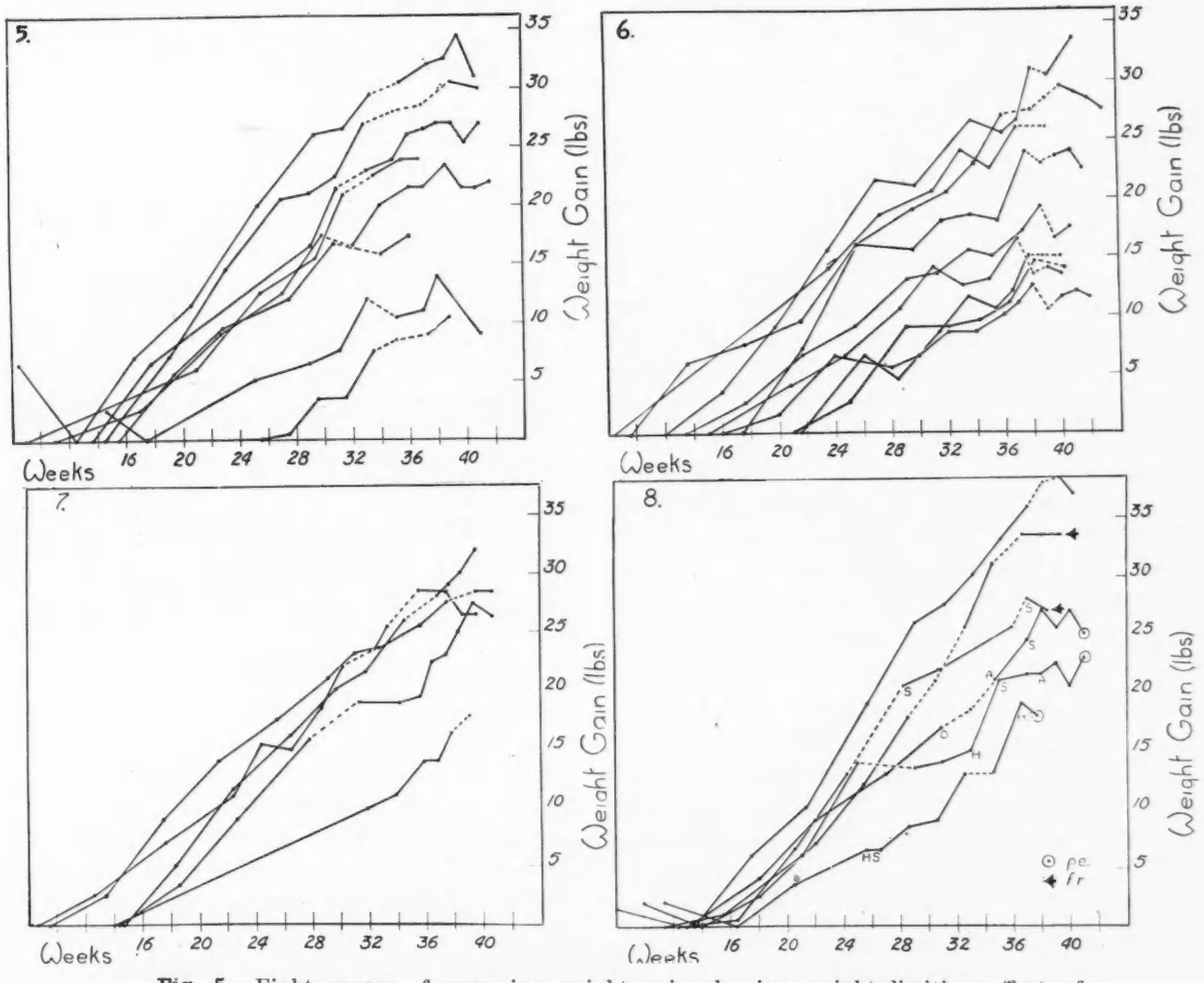


**Fig. 5.**—Eight curves of excessive weight gain showing weight limiting effect of œstrogenic therapy (broken lines); first course of treatment was given between 30 and 36 weeks. **Fig. 6.**—Nine curves of excessive weight gain showing weight limiting effect of œstrogenic therapy (broken lines); first course of treatment was given after 36 weeks. **Fig. 7.**—Weight gain curves of five patients who showed little response to therapy (broken lines). **Fig. 8.**—Six miscellaneous curves of excessive weight gain: three patients became eclamptic (p.e.); two show increased weight increment (f.r.); top curve shows complete lack of response to rigid dietary regimen. Period of œstrogenic therapy is indicated by broken lines. Symbols: S—magnesium sulphate; H—increased blood pressure; A—albuminuria; O—œdema.

In some cases a repetition of the drug might have been used, but was withheld because the patient was approaching or had passed her expected date. In other cases a weight loss appears in the last two weeks of pregnancy, as is claimed by some observers,[4, 6] but this is not a constant observation in the series. No unusual deviations from the accepted course of labour were noted in any of the patients, nor were any macroscopic changes evident in the placentæ. This would sugest that the administration of œstrogens as a method of limiting excessive weight gain during pregnancy is apparently free from deleterious effects on the patient and the fetus.

Chesley[4] has shown in an exceedingly comprehensive and analytical article on weight gain during pregnancy that variations within normal limits for all trimesters are innumerable, thus precluding any set pattern of weight behaviour for any individual or group. Therefore it cannot be definitely stated that any weight-limiting therapy is the sole factor in a change of weight gain pattern. This variability is shown in the graphs here presented in which some patients appear to have a carrying-over effect from a two week period of œstrogenic therapy, whereas others show a steady rise in weight increment following a definite halt while taking the hormone. In the cases where more than one course of therapy was given, the periodic inhibition of gain is noted with a consistency that suggests more than fortuitousness. Because of the unpredictable weight gain pattern in pregnant women, and individual variations, it is impossible to run a parallel clinical control series; this could be done only by biochemical assays of blood and urine œstrogen levels.

It has been shown by Cohen, Marrian and Watson[5] that œstrogens excreted in the urine of pregnant women are in both combined and free forms, and as the level of the former type falls, the level of the latter rises. The most marked rise of the free œstrone and œstriol appears to coincide with the imminent onset of labour. This gives rise to the speculation as to whether a diuresis accompanies the excretion of the free substances, which might account for a pre-labour weight loss; this could explain the extraordinarily high urinary output immediately preceding labour that is shown in Fig. 2. It also brings up the question of the metabolic fate of ingested œstrogens in an organism which is already manufacturing them at an exceedingly high level.[3]

It is not the purpose of this presentation to go into the factors governing the retention of extracellular and intracellular fluids during pregnancy. It is well known that these involve the storage and excretion of sodium, potassium and nitrogen, and the metabolism of the sex steroids by the liver. However, the clinical results that have been observed suggest that further investigation and assessment of the rôle of the œstrogens in the matter of fluid retention is warranted.

I wish to express my sincere gratitude to Dr. Harriet Perry-Lederman for her co-operation and interest throughout this study.

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## HEREDITARY, FAMILIAL AND ACQUIRED PTOSIS OF LATE ONSET

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THE purpose of this paper is to attract the attention of neurologists and ophthalmologists to a disease already described but not very frequent and not well known by the practitioner and even by those two groups of specialists. We do not claim that our observations contain the complete data of the familial anamnesis and the most important laboratory investigations.

All the patients, except one, were examined by us at the request of ophthalmologists. And that would confirm, if necessary, the very judicious opinion that Neilsen expressed recently.

"The neurologist serves the general practitioner as a diagnostician and as a means of placing therapy on a sound basis. He serves the otolaryngologist and the ophthalmologist in distinguishing when a disease at first limited to one region of the body invades the brain. He serves the orthopedist in differential diagnosis of painful conditions and in diseases of the muscles. He serves the general surgeon in differentiating functional abdominal states from surgical ones. The anæsthetist refers cases when complications arise. The obstetrician refers both mother and baby for trauma at birth. The urologist asks for help in suspected neurogenic bladder, the radiologist for interpretation of etiology of roentgenologic conditions. Even the psychologist and the electroencephalographer ask for help. Last, but not the least, the Industrial Accident Commission constantly needs a neurologic survey of traumatic cases. . . ."[1]

We were necessarily handicapped in our investigation, since we had only one examination at our private office, except for two patients: one came once to the Neurological Outdoor Department of Notre-Dame Hospital, the other came twice to our office. In spite of this insufficiency of data, our findings present some interest, either in corroborating what has already been published on the subject in some rare articles, or emphasizing some associated phenomenon of which we could not explain the relation with the ptosis, but of which we could not also deny the presence.

The hereditary ptosis of late onset is a real disease as it was described by Dutil in 1892: that we intend to demonstrate. We give a summary of the observations and mention the only abnormal findings. We do not dwell on the description of the ptosis, bilateral in these cases, or on the attitude and the mimic expression of the patients. They are all similar, and they have a family likeness which might be termed a "camel-like" appearance. When the ptosis is marked they contract their frontalis in order to supply the deficiency of the levator, and they tilt their head backward in order to get the pupils in line with the narrowed palpebral opening.

The hereditary ptosis is usually congenital and associated with ocular dystrophies, malformations or functional troubles, and with ophthalmoplegias (nystagmus, symblepharon, microophthalmus, coloboma, cataract, oculo-motor paralysis especially of the superior rectus and internal rectus).[2]

The acquired type of the hereditary ptosis is much rarer. As in the cases reported by Forsberg,[3] Faulkner,[4] in some cases of Spencer[5] and of Meumann,[6] this acquired ptosis can appear during the three first decades of the patient's life. But its onset can be much later: around forty and more often around fifty and sixty. This type of ptosis has been observed by Gowers.[7] Fuschs, quoted by Dutil, presented in 1887 two patients at the Medical Society of Vienna who had an acquired ptosis of late onset without mentioning if the ptosis was hereditary.

Hereditary ptosis of late onset was really described by Dutil in 1892.[8] In his paper, he reported the case of an hereditary ptosis of late onset, observed in the service of Charcot, belonging to a family in which seven members distributed in four generations had a similar abnormality of the eyelids developed after the fiftieth year of their life. There was or has been no other abnormality of the eyes. He was dealing then with a pure hereditary and familial ptosis of late onset. This type of ptosis is denominated by some French authors: "le ptosis tardif de Dutil". Dutil stated that he had no knowledge of similar cases reported in the literature, except the communication of Fuschs.

In 1903, Delord[9] published a short paper regarding a familial offspring of 3 generations in which 8 members had a bilateral ptosis after their fortieth year of age; they had no other ocular abnormality. In 1923, A. Boulanger[10] discussed the matter in his thesis, laying stress on the hereditary character of the disease, on its dominant type of transmission, on the fact that the transmissibility of the disease has no relation to sex and that the ptosis is exclusive of any other ocular disturbance.

Forsberg, in 1932, reported 13 cases of acquired ptosis in a familial offspring of five generations concerning 67 persons. The ptosis was hereditary, familial and acquired, but not of late onset since it had developed from six to 22 years of age. It was the only ocular disturbance, it was not related to sex, in two cases it was transmitted by a normal parent, which apparently does not fit in with the dominant type of transmission. Frank Rodin and Hans Barkan[11] published an important review on hereditary ptosis; in fact the first on the matter. The authors divide this type of ptosis into four categories as follows: (1) hereditary and congenital ptosis; (2) hereditary ptosis with ophthalmoplegia externa; (3) non-congenital hereditary ptosis; (4) hereditary ptosis with epicanthus. They place the hereditary ptosis of late onset in the third category and mention the publication of Dutil, Delord and Boulanger.

They also make mention of an article of Spencer,[12] published in 1917, relating the case of a ptosis with some ophthalmoplegia externa.

The ptosis had developed around the 15th year of age; the mother, two sisters of the mother, and a brother of the patient had the same disturbance. The ptosis of the brother appeared around 22. The ptosis was hereditary, familial but not of late onset and not exclusive. The same authors make mention also of a paper of Meumann[13] published in 1925 in which he reports a family pedigree of five generations; 22 of 32 members had a ptosis acquired late, developed mostly between 40 and 50 years of age, two only between 24 and 30.

The cases of Faulkner[14] were the father, two sons and two daughters; the ptosis of one daughter developed during childhood, the ptosis of the three others appeared after the 30th year of age. The ptosis of all these cases was associated with a marked ophthalmoplegia externa, especially regarding the upward ocular movement. It could be integrated with the second group of Rodin and Barkan and is not exactly similar to the ptosis of our cases which, except in one case, was pure. Since the important review of Rodin and Barkan and the article of Faulkner, we have not found any publication in the literature dealing with the hereditary and acquired ptosis.

CASE 1

Mrs. D.M., aged 72, was referred to my office on December 10, 1941, for a bilateral ptosis which she developed when she was 55 years old. (1) Father: bilateral ptosis which had its onset when he was 50 years old. Difficulty in swallowing. (2) Two sisters of the father (Known by the patient—of 3): (*a*) one had slight bilateral ptosis with difficulty in swallowing. Died at 56. (*b*) The other had bilateral ptosis. Onset around 50. No difficulty in swallowing. (3) One brother of the father (Known by the patient—of 4): bilateral ptosis at 50. Difficulty in swallowing. (4) Eleven sisters and brothers: 5 died infants or children, 4 normal: 56, 57, 58, 66. One bilateral ptosis. Onset around 50-55. Normal deglutition. Died. One bilateral ptosis. Aged 70. Onset at 60.

Marked difficulty in swallowing. For the last eighteen years has been operated on four times on the right side, twice on the left for the ptosis. Difficulty in swallowing appeared when patient was 56 years old: worse in the last six years and chiefly regarding solid food. No other disturbances of the muscles of the eyes (intrinsic and extrinsic). Fundi and pupils are normal. Reflexes of pharynx and velum are sluggish. Somatic examination negative. Blood pressure 170/100. We saw the patient again in 1946; she was in the same condition, except that deglutition was more difficult and that there was slight diplopia in the gaze towards the right without any appearance of the slightest strabismus.

CASE 2

Patient (female) examined at the Outdoor Department of Neurology of Notre-Dame Hospital during 1941. Aged 64; bilateral ptosis. Onset around 59. (1) Father's mother: normal. (2) Father's father: not known by the patient. (3) Mother: normal. (4) Father: bilateral ptosis. Onset around 60. (5) Two father's brothers: (*a*) one normal: four normal descendants. (*b*) One bilateral ptosis. Onset around 50 to 60. (6) One brother died at 58: Bilateral ptosis. Onset around 50. (7) One sister aged 67: normal. One daughter: normal. One daughter: bilateral ptosis. Onset between 50 to 60. One son: bilateral ptosis. Onset between 50 to 60. No other disturbances of the eyes. No neurological or somatic abnormalities.

CASE 3

Mr. J. L., 67, examined October 23, 1942. Bilateral ptosis for three years, first on the left side and since a year on the right. (1) Father died at 67 without ptosis. (2) Mother died at 97 without ptosis. (3) Aunts and uncles known: no ptosis. (4) One brother died at 42 without ptosis. (5) One sister: aged 85. Bilateral ptosis. Onset around 75. (6) Three sisters died: 24, 25 60. No ptosis. (7) Three descendants: Normal.

Difficulty in swallowing for the last 6 or 7 years mostly as regards solid food which he cuts in very small pieces. Was treated for goitre 10 years ago. The speech is nasal, but the velum moves apparently normally and the reflexes of the velum and the pharynx are present. Vertical movements of the eyeballs are almost absent especially upward. Limitation of the lateral movements. Pupils, vision, fundi normal. Somatic and neurological examination negative. Blood pressure 140/70.

CASE 4

Mrs. L., aged 53. Examined during 1942. Bilateral ptosis for five months, mostly on the right. (1) Father: died at 62. Bilateral ptosis. (2) Mother: died at 87. Normal. (3) Father's brothers: one died at 72 without ptosis. One died at 69 without ptosis. Father's sisters: One died at 18. No ptosis. One died at 45. No ptosis. One died at 60. Bilateral ptosis.

Blood pressure 180/105. Somatic and neurological examination negative. Normal vision, fundi, extrinsic and intrinsic muscles of the eyes. Normal pupils. Ptosis was apparent on the right, normal deglutition.

CASE 5

Mr. J. L., 69. Was examined on June 2, 1942. Bilateral ptosis for the last 8 or 9 years. Head tilted backward since last year, in order to improve the vision. (1) Mother: Bilateral ptosis. Onset around 60. Difficulty in swallowing. (2) Three sisters and four brothers of the mother: Patient remembers that one uncle had bilateral ptosis around 55 or 56. The patient did not know if the other uncles and the aunts had blepharoptosis or not. (3) Four living sisters: One sister has a bilateral ptosis. Onset around 55. Mostly on the left side. (4) Three living brothers: One brother has a bilateral ptosis. Onset around 52.

No diplopia. Normal fundi and vision. Normal pupils. No neurological signs. Slight limitation of the lateral movements of the eye. More marked limitation of the upward gaze. Somatic examination negative. Blood pressure 140/80. For the last years, difficulty in swallowing fluids. Reflexes of the pharynx and velum are present.

CASE 6

Mrs. N.M., aged 57. Admitted to Notre-Dame Hospital, October, 1943. Bilateral ptosis since 4 or 5 years. Head tilted backwards for facilitating the vision. Normal deglutition. (1) Father's mother: bilateral ptosis for which she had been operated on. Onset about 50. Three sisters and one brother of that grandmother have been known by the patient; they had no ptosis. (2) Father: Bilateral ptosis. Onset about 50. Has been operated on for that ptosis 4 or 5 years after the onset. (3) One father's brother died at 60 without ptosis. Ten descendants: three have reached 50 and were without ptosis.? (4) Three father's sisters: one living, 70, without ptosis, one died at 70, no ptosis. One died at 26, no ptosis. (5) Four brothers: 71, 53, 44, 35. No ptosis. (6) Five sisters: 38 to 52. No ptosis.

No neurological signs. Normal fundi and pupils. Normal intrinsic and extrinsic muscles of the eyes. No somatic disturbances.

### CASE 7

Mr. A.B., 56. Was examined at my office on March 11th, 1944, for bilateral ptosis. (1) Mother's mother: Bilateral ptosis. Onset? Died at 70-75. Used to lift her eyelids with her fingers. (2) Mother: Bilateral ptosis. Onset around 50. (3) Six mother's sisters and brothers: two have reached 60. No ptosis. (4) Two brothers: One 64, no ptosis. Three normal daughters. One 66, bilateral ptosis. Onset 54. (5) Three sisters: 30, 35, 40. No ptosis.

Palpebral opening of about ¼ cm. No other signs or symptoms. Flabby eyelids. Fatigue would increase the ptosis. Vision and fundi normal. Intrinsic and extrinsic nuscles normal. Normal deglutition. Neurological and somatic examination negative. Test with parenteral prostigmin was negative regarding the ptosis.

### CASE 8

Mrs. E.C., 64. Was examined by me during February, 1945. Bilateral ptosis since 7 or 8 years. (1) Father: Bilateral ptosis. Onset before 50. (2) Mother: No ptosis. (3) Father's sisters and brothers: Only aunts known by the patient: One aunt: Bilateral ptosis. Onset around 50. No children. One aunt: No ptosis. Normal descendants. (4) One brother: Bilateral ptosis. Onset 40. (5) No sisters, no other brothers.

Difficulty in swallowing since 4 or 5 years. Blood pressure 160/100. No neurological signs. Somatic examination negative. Fundi, vision, intrinsic and extrinsic muscles of the eyes, normal. Patient's condition better during the evening than in the morning.

### CASE 9

Sister M., aged 60, was examined on June 30, 1948. Progressive bilateral ptosis for the last 5 or 6 years. (1) Father's mother: bilateral ptosis. (2) Father: died at 54 without ptosis. (3) Mother died at 78 without ptosis. The patient did not know her uncles and aunts who are all dead, nor their children. (4) Two sisters: one died at 58, bilateral ptosis; the other died at 48 without ptosis. (5) Three brothers still living: 48, 58, 65, without ptosis.

Difficulty in swallowing solid food unless fluid was taken at the same time. The voice of the patient is weaker and she cannot control its tonality; sensation of burning and tingling in the laryngeal area.

The ptosis is more marked in the morning; the patient had to lift her eyelids, especially the left, with her fingers. Normal mastication. The movement toward the internal angle of each eye is very slightly limited; the upward movement is almost abolished. The reflex of the velum is normal. Motility of the pharynx is weak and its reflex is almost absent. No neurological signs elsewhere. Blood pressure 150/90. Prostigmin test is negative.

### COMMENT

These cases prove, we think, that the hereditary, familial and ptosis of late onset does really exist as it has been suggested by Dutil. That ptosis is usually pure, without any other ocular disturbance, without any neurological signs or symptoms, except, however, the disorder of swallowing about which four of the patients complained and which was present also, as affirmed by one patient, in four of the six members of her family who had a ptosis . We mention this abnormality but we cannot explain the mechanism of its relation to the concomitant ptosis. In one family, the ptosis was familial but not hereditary, but it might have developed in the father if he had lived older than 67 years of age. It is true that the ptosis developed at 64 on the patient, but in one of his sisters it appeared when she was 75 years old. It could have developed at the same age in the father. The same explanation could be given regarding the father of case 2.

As usual, regarding the genealogy of hereditary diseases, our data were uncompleted and were exclusively established from information given by the patients, who very often did not know their ancestors even their grandmothers or grandfathers, who could not inform us regarding some of their uncles, aunts and cousins whom they never met or had not seen for a long time. However, the type of ptosis we are dealing with seems to have a dominant hereditary character which is not related to sex. In one case only, it was associated with oculo-motor disturbances which were a palsy of the superior rectus and a paresis of the horizontal ocular movements of the eye-balls.

One is led to believe that hereditary ptosis of late onset is due to a myopathy of the levator of the eyelid as was suggested by Fusch. Indeed, it can be hardly admitted that a degenerative process can be exclusively and indefinitely limited to the cellular group of the third cranial nerve nucleus which gives innervation to the levator.

In three of our cases (3, 5, 9), as in others reported in the literature, the superior rectus is either the only one disturbed, or the most greatly paralyzed of the extrinsic ocular muscle.

The embryonic origin of the levator and of the superior rectus is the same. Actually, the levator, of late differentiation, comes off the internal border of the superior rectus already formed. And it occupies its definitive position around the fourth month of the embryonic life. Their common origin may predispose them to a common myopathic process. By analogy, it is not unreasonable to admit the possibility of a myopathic process of the extrinsic ocular muscles, and we remember two cases of myotonia atrophica in which we observed paresis and even paralysis of the oculo-motor muscles. And we do not believe that some other process than a myopathy of the ocular extrinsic muscles can be admitted to explain such disturbances in a

disease like myotonia atrophica, which, besides, gives rise to myopathy of such muscles of the head as the levator itself, the fascial muscles, the masseter, the sterno-cleido-mastoid. In our cases, we did not find any other etiological agent than heredity.

Certainly, in each case, we must consider the possibility of myasthenia gravis and especially in the cases with difficulty in swallowing, but only to reject that possibility. In none of them could the essential phenomenon of muscular exhaustion be found. In one case, the prostigmin test was negative. Myasthenia is not a familial and hereditary disease.[15] No patient complained of fatigue or weakness of the muscles of the neck, of the limbs, of the mastication. There was also no diplopia, except in one case, in whom it was slight, without increasing during the day and of late development regarding the age of the ptosis.

There is no disease of the central nervous system which can give rise exclusively and indefinitely to a familial and hereditary ptosis. So, we think that our cases are of the same type as the first one described by Dutil and that the ptosis is due to a myopathic process of the levator without prejudging the origin and the nature of the original cause, which is a problem of genetics.

Once more, this study is perhaps more ophthalmological, but it finds its place in neurology, and that is so true that our eight cases, except two, were sent to us by ophthalmologists who wanted to know if the ptosis of their patients was not due to a neurological process and to be sure of a definite diagnosis.

SUMMARY

We report the observation of 9 patients who had a bilateral ocular ptosis. The ptosis was familial, hereditary in all cases and appeared after 50 years of age. It was pure in all patients, except some limitation of the upward gaze in 3 cases. The etiology is genetic and it can be assumed with likelihood that the mechanism is myopathic. Some difficulty in swallowing was associated with the ptosis, having apparently the same hereditary character. Some historical data are given which permit the naming of this type of ptosis, as French authors do: "le ptosis tardif de Dutil".

I am indebted to Dr. Jules Brault and especially to Dr. François Badeaux for having given me the opportunity of examining their patients and publishing the results of this clinical study.

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## NEOHETRAMINE AND THEPHORIN: TWO NEW ANTIHISTAMINIC DRUGS*

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RECENT interest in antihistaminic drugs has brought forth several new synthetic products which have shown potent antihistaminic and antianaphylactic properties. Two of these new drugs which we have tested[1, 2] are thephorin (2-methyl-9-phenyl-tetrahydro-1-pyridindene) and neohetramine (2-(N-dimethylaminoethyl-N-p-methoxybenzyl)-amino-pyrimidine mono-hydrochloride). These were investigated by us in the laboratory to determine their antihistaminic and antianaphylactic properties.

It had been determined that the 100% lethal dose of histamine base for guinea pigs when injected intravenously was 0.4 mgm. per kg. of body weight. These animals were protected by injecting them intraperitoneally with 3 mgm. per kg. of body weight of the antihistaminic drug fifteen minutes prior to the injection of histamine. The 100% lethal dose now required in the presence of this amount of neohetramine was 2.5 mgm. per kg. of histamine base, or 6 times the lethal dose. The amount of histamine base necessary for 100% fatalities in the presence of thephorin was 4.5 mgm. per kg. or 11 times the original lethal dose. Other workers have shown that under the same circumstances the lethal dose of histamine necessary in the presence of

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antergan is 2.4 mgm. per kg., in the presence of neoantergan is 15 mgm. per kg., in the presence of benadryl is 2 mgm. per kg. and in the presence of pyribenzamine is 15 mgm. per kg.[3]

Studies were carried out to show the protective effect of these drugs against histamine using the Schultz-Dale bath with guinea pig intestinal strips. One gamma per c.c. of histamine base gave an excellent contraction. This contraction was completely inhibited by adding a concentration of 5 gamma per c.c. of neohetramine, or 2 gamma of thephorin to the bath. Others have determined that 2.5 gamma of antergan, 1 gamma of neoantergan, 5 gamma of benadryl are each capable of the same inhibition.[3]

Guinea pigs which were actively sensitized to horse serum were used to show the protective properties of these two agents against fatal anaphylactic shock. It was found that 4 mgm. per kg. of thephorin protected 67% of the animals and 5 mgm. per kg. of neohetramine protected 100% of the animals from fatal anaphylactic shock in our series. Four mgm. per kg. of thephorin protected 92% of a series of passively sensitized animals from fatal anaphylactic shock. These results were similar to those obtained by other investigators using other antihistaminic drugs.[4]

Observations were made on the intestinal strip of guinea pigs which had been adequately sensitized with horse serum using the Schultz-Dale bath. When 0.5 c.c. of horse serum was added to the bath, a marked contraction of the strip ensued. It was found that 0.025 gamma per c.c. of thephorin added to the bath inhibited this contraction. Neohetramine did not inhibit the contraction in the concentrations we used. It had been shown that the inhibition of this contraction can also be accomplished by 0.025 gamma per c.c. of benadryl, or 0.025 gamma per c.c. of neoantergan.[4]

It is apparent that both these drugs had good antihistaminic properties, both *in vivo* and *in vitro*. In this respect they compare favourably with the other available drugs. Thephorin has good antianaphylactic properties, both *in vivo* and *in vitro*, and neohetramine has good *in vivo* antianaphylactic protective ability.

Clinical studies were now done to determine their toxic properties, their anti-whealing ability, their effect on the spirometric readings of asthmatic patients, and their value in the allergic states.

Toxicity studies were performed on patients who had been hospitalized. Thirty-seven patients received 300 mgm. per day of thephorin for 4 days and 17 patients received 300 mgm. per day of neohetramine for 4 days. Urinalyses, complete blood counts, blood pressures and electrocardiograms were taken before, during and after medication. No significant changes were noted. In one of these cases, a seventy-year old patient with heart failure who took thephorin, the T wave in CV4 became inverted. This reverted back to normal upon withdrawing the drug. On readministration of the drug the T wave again became inverted. Another patient, who took thephorin, a sixty-five year old man with arteriosclerotic heart disease, showed an inverted T wave during the administration of the drug. The T wave became upright after the medication was discontinued. It should be noted however that these changes occurred only in patients with heart disease and were reversible. No other abnormal electrocardiogram findings were noted in any of the other patients taking this very high dose of thephorin.

Eight patients were hospitalized and electroencephalograms were taken on each. Then 2 patients received 200 mgm. daily of benadryl, 2 patients received 200 mgm. daily of pyribenzamine, 2 received 200 mgm. daily of thephorin and 2 received 200 mgm. daily of neohetramine. On the second day the electroencephalograms were repeated. No significant observations were made in relation to the original tracings except a sporadic increase in activity in those taking the drugs. No significant evaluation could be made.

In order to test the effect of these drugs when taken orally, on whealing formation, ragweed sensitive patients were skin tested with both ragweed and histamine. The wheals which formed in ten minutes time were recorded. These same patients were given 200 mgm. of pyribenzamine orally and in one hour the skin tests were repeated and again recorded. This same procedure was repeated the following day using 200 mgm. of neohetramine, and again reported the next day using 200 mgm. of thephorin. It was noted that all the drugs inhibited the size of the wheal and flare. In order to show that these drugs locally inhibited the whealing reaction caused either by histamine or by the antigen antibody reaction, ragweed sensitive patients were again skin tested with ragweed antigen and histamine. These wheals were recorded in ten minutes'

time. It was shown that when neohetramine was mixed with histamine or with ragweed so that there was a final concentration of 0.25% of the drug in the same solution prior to the intradermal injection, the whealing formation was inhibited. If thephorin was mixed with histamine or with ragweed so that there was a final concentration of 0.25% of the drug in the same solution prior to the intradermal injection, the whealing formation was inhibited.

Spirometric studies were carried out on 13 cases of different kinds of bronchial asthma who took thephorin and 21 cases of different kinds of bronchial asthma who took neohetramine. All

TABLE I.
CLINICAL EFFECT OF NEOHETRAMINE

| *No. 243* | *Diagnosis* | *None* | *Slight* | *Moderate* | *Complete relief* |
|---|---|---|---|---|---|
| | | % | % | % | % |
| 124 | Hay fever..... | 18 | 22 | 27 | 33 |
| 41 | Allergic rhinitis. | 20 | 27 | 24 | 29 |
| 33 | Bronchial asthma..... | 37 | 24 | 27 | 12 |
| 11 | Atopic dermatitis.... | 18 | 73 | 9 | 0 |
| 20 | Urticaria..... | 25 | 25 | 20 | 30 |
| 6 | Migraine..... | 17 | 33 | 0 | 50 |
| 8 | Contact dermatitis.... | 0 | 38 | 50 | 12 |

TABLE II.
CLINICAL EFFECT OF THEPHORIN

| *No. 382* | *Diagnosis* | *None* | *Slight* | *Moderate* | *Complete relief* |
|---|---|---|---|---|---|
| | | % | % | % | % |
| 180 | Hay fever..... | 10 | 14 | 32 | 44 |
| 71 | Allergic rhinitis. | 17 | 9 | 39 | 35 |
| 71 | Bronchial asthma..... | 45 | 28 | 11 | 16 |
| 16 | Atopic dermatitis.... | 25 | 56 | 13 | 6 |
| 30 | Urticaria..... | 27 | 13 | 17 | 43 |
| 6 | Migraine..... | 33 | 50 | 17 | 0 |
| 8 | Contact dermatitis.... | 0 | 50 | 38 | 12 |

these were cases of active asthma. Their vital capacity was determined immediately prior to the administration of the drug. They were then given orally a triturated tablet of 50 mgm. of the drug being used. Of those taking thephorin, 6 of the 13 had an increase in vital capacity within one-half hour. In one hour 8 cases had an increase in their volume, but only 3 had an increase of at least 25% of the original reading. Only 2 cases noted any clinical improvement and one became worse. Of those who took neohetramine, 6 of the 21 had an increase of at least 25% of the original reading. Nine cases had clinical improvement. As noted by others[5] no definite correlation could be made as to the type of asthma and the increase or decrease of vital capacity, nor could any true clinical conclusions be drawn from the spirometric examinations.

Thephorin is available in coated tablets containing 25 mgm. of the drug. Neohetramine is available in 50 mgm. tablets which are scored. The dose in the evaluation studies was one tablet of the drug every 4 hours as needed. A total of 249 patients took neohetramine and a total of 389 patients took thephorin. Relief when obtained from neohetramine lasted approximately 3 to 6 hours and with thephorin approximately 2 to 5 hours. Results from clinical trial in allergic states were divided into "No relief", "Slight relief", "Moderate relief" and "Complete relief". Results from clinical trials in allergic conditions are listed in Tables I and II. Because many patients received concomitant therapy, benefit was recorded by comparison with periods when the drug was not taken.

In seasonal hay fever it was noted that only 18% had no relief and in perennial allergic rhinitis only 20% had no relief, when using neohetramine. With thephorin, only 10% had no relief in seasonal hay fever and only 17% had no relief in perennial allergic rhinitis. These results compare favourably to those obtained from the other drugs.[3]

In asthma neohetramine gave some benefit to 39%; thephorin gave relief in 27% of the cases; pyribenzamine has been recorded as giving relief in 28%.

In atopic dermatitis, neohetramine gave slight relief in 73% of the cases, moderate relief in 9%; thephorin gave slight relief of the pruritus in 56%, moderate relief in 13% and complete relief in 6%

Thephorin gave relief to patients that had urticaria and angioneurotic œdema in 73% and in 75% who took neohetramine relief was observed.

Of the patients with contact dermatitis who took neohetramine, 12% had complete relief and 50% moderate relief; of those that took thephorin 38% had moderate relief and 12% complete relief.

The drugs were also used in a miscellaneous group and it may be seen from the tables that some benefit was obtained in migraine headaches. One case of Schonlein's purpura received relief by taking either of the drugs after ingestion of

the offending foods. Two cases of serum disease received relief from either of the drugs. In cases of pruritus ani and acne rosacea there was no benefit.

Both of the two drugs were seen to have a low percentage of side-reactions. In this series 23% of the total number of patients who took thephorin had side reactions, and only 10% of the total number of patients who took neohetramine had side effects. These reactions are tabulated in Tables III and IV. This compares favourably to benadryl which gave reactions in approximately 50% of the cases and pyribenzamine which gave reactions in 23% of the cases. The other

TABLE III.
NEOHETRAMINE SIDE EFFECTS 10% OF TOTAL

| *Side reactions* | *Percentage of total reactions* |
|---|---|
| | % |
| Nervousness | 24 |
| Nausea | 16 |
| Insomnia | 16 |
| Drowsiness | 16 |
| Dizziness | 8 |
| Diarrhœa | 8 |
| Constipation | 8 |
| Headache | 4 |

TABLE IV.
THEPHORIN SIDE EFFECTS 23% OF TOTAL

| *Side reaction* | *Percentage of total reactions* |
|---|---|
| | % |
| Nervousness | 22 |
| Nausea | 22 |
| Insomnia | 10 |
| Drowsiness | 9 |
| Headache | 9 |
| Constipation | 8 |
| Urinary symptoms | 6 |
| Dryness of the mouth | 3 |
| Dizziness | 2 |
| Sweating | 2 |
| Nervous chills | 2 |
| Sore throat | 2 |
| Depression | 1 |
| Diarrhœa | 1 |
| Nightmares | 1 |

histamine antagonists differed in their side reactions in that they often caused drowsiness. The side effects, when they appeared, of these two drugs were nervousness and insomnia, which may be compared to a benzedrine like effect. Patients who have taken these drugs in the treatment of coryza found side reactions to be advantageous, for they felt elated.

Thephorin and neohetramine are seen to be useful antihistaminic agents. Their clinical value is similar to that of the other antihistaminic drugs in that they portray good therapeutic effect in allergic rhinitis, both perennial and seasonal, urticaria and angioneurotic œdema. Both drugs have some value in the management of asthma, atopic and contact dermatitis. Their value is enhanced because of the low percentage of their side effects.

SUMMARY

Thephorin and neohetramine have good antihistaminic and antianaphylactic properties. They compare favourably with the other histamine antagonists in their clinical value in allergic states. They have a low percentage of side reactions.

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## INFECTIOUS POLYNEURITIS AND RELATED SYNDROMES*

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THE type of polyneuritis to be discussed shows widespread symmetrical flaccid paralysis, loss of the deep reflexes, frequent cranial nerve involvement, inconstant changes in the superficial reflexes, paræsthesias with or without objective sensory disturbances, occasional autonomic system alterations, and most constantly, an increased spinal fluid protein in the absence of a cellular response.

### ETIOLOGY

The causal factor in the published cases and in those comprising this study has not been determined. About a half seem to follow infection in some part of the respiratory tract. It is generally assumed that in a patient with polyneuritis where lead, alcohol, arsenic, diphtheria and certain vitamin deficiencies can be excluded, a virus explanation is the best that can be offered at the present time.

None of the ordinary focal infections lead to this syndrome and it is a fact that the surgical handling of a focus of infection has never resulted in a spectacular improvement in any of

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the cases so far reported. One of our patients with infected teeth showed no change for the better after their removal. Another man of 29 with a large infected pyonephrotic kidney developed a symmetrical flaccid paralysis with 90 mgm. of protein in the spinal fluid. In view of the constant pyuria and the progressive weakness, we advised removal of the kidney. The mass was so large and so fixed that surgery could not be carried out. The man made a good recovery from his neurological difficulties and he continues working without having his kidney removed.

The relation of this kind of polyneuritis to encephalitis, myeloradiculitis, and neuro-myelitis optica (all of which are considered to be of viral origin) must be very close. Not a few patients will at some time show features pointing to cerebral, spinal cord, or optic nerve affection. As a rule the majority of the cases can for clinical purposes be thought of as peripheral in character, but we must remember that the distinction is somewhat artificial and that in most of the severe ones there is involvement of the central nervous system neurones—although this may not always be of such a nature as to be irreversible.

## CLINICAL FEATURES

The proximal and distal muscle groups of the extremities, and the muscles of the trunk, back, neck, abdomen and chest may be paralyzed. In the severe cases the patient cannot move the extremities, raise his head, feed himself, or turn in bed. Individual muscles are never affected. Frequently there is facial weakness on one or both sides. The muscles of mastication and those supplying eye movements are rarely involved. It is very common to have weakness in the bulbar area with resulting palsy of the palate, difficulty in swallowing, and in talking. The dysphagia and dysphonia are among the first symptoms to disappear if the case progresses favourably. The diaphragms do not often share in the paralysis. Sphincter changes are fortunately rare and when present are of short duration—they are ascribed to changes in the sacral nerves. The degree of paralysis may fluctuate widely for no obvious reason when the course is chronic. Once power begins to return in the favourable case the progress is often very rapid. Of value in differential diagnosis—especially where poliomyelitis is to be considered—is the fact that muscle atrophy is not likely to occur in the acute or even in the chronic case.

In the sensory field the most constant symptom is tingling or numbness in the feet and hands or even the tongue and face. This often precedes by days or weeks the onset of motor weakness. A decrease in sensory perception for one or several modalities is easily demonstrated in a stocking-glove distribution in many of the patients. Muscle tenderness is not uncommon. In at least half of the cases there is a moderate amount of pain in the back, neck, extremities, and head. Sometimes the pain is intense and persistent and it may mask the more silent state of muscular weakness for several days. Blurring of vision points to optic nerve involvement and it may be associated with papillœdema.

Autonomic system features in the form of causalgic pain, redness of the hands and feet, and profuse sweating of the palms and soles may be encountered. It is likely that irritation of the sympathetic fibres in some part of their course may give rise to such effects. When present they are likely to be more lasting than the associated muscle paralysis.

There may or may not be a low-grade fever in cases not complicated by pulmonary infection. Changes in the white blood count and an increased sedimentation rate take place sometimes without other cause than the neurological condition, but in the majority no significant alterations are met with.

Of greatest help in diagnosis is some combination of the features mentioned above along with the spinal fluid changes that were first pointed out in 1916 by Guillain, Barré, and Strohl. There will be an elevation of the spinal fluid protein ranging between 50 and 2,000 mgm. %. With this change in protein there is not likely to be any increase in cells and this accounts for the so-called "albumino-cytologic dissociation". With the elevation in protein there is often a first or mid zone curve in the colloidal gold pattern. In some cases the spinal fluid pressure may be elevated.

## PROGNOSIS

Mortality figures vary between 14 and 42%. Out of 24 cases we have had 9 deaths—4 within a month and 5 others within a year. The immediate outlook in any individual case depends on the rate of onset and the distribution of the paralysis. The chief danger naturally comes

with extension to the chest and bulbar zones. Very sudden changes should always suggest involvement at the bulbar level. The age of the patient does not seem to influence the prognosis very much. Recourse to a Drinker respirator may in an occasional instance be life-saving. It is always unwise to give a good prognosis until the first two or even four weeks have been accomplished. The chances of a good recovery after six months of paralysis must always be at least uncertain, especially if pain is a prominent feature. Spinal fluid changes do not aid in our forecast and there may be a protein increase for many months after clinical cure has been established. Once a patient recovers and remains completely well for a month recurrence is very unlikely.

### DIAGNOSIS

Poliomyelitis should be considered when there is an asymmetrical distribution of the paralysis, when individual muscles suffer, if atrophy occurs rapidly in the paralyzed areas, and where the spinal fluid shows a cellular response. The maximal paralysis is likely to be noted earlier in poliomyelitis than in polyneuritis.

The known types of polyneuritis do not call for special comment, because the distribution and symptomatology of the paralysis in poisoning with lead, arsenic, alcohol, and in the deficiency. states is so classical. However, much confusion often arises around the question of diphtheria. It may give a symmetrical polyneuritis coming on between three and eight weeks after the beginning of the infection in the pharynx. This will almost constantly have been preceded by paralysis of the soft palate in the second week and blurring of vision in the third week (ciliary muscle palsy). As in infectious polyneuritis of unknown etiology the duration of the paralysis may be between two months and a year. The isolation of organisms from the pharynx and a positive Schick test would make the diagnosis pretty certain. The differentiation once polyneuritis has occurred is largely of academic interest since the treatment of diphtheritic and virus polyneuritis is the same. The diphtheria antitoxin only helps in preventing neuritis if used in the first three days of diphtheria and it therefore has no place in the management of the nerve complications.

Periarteritis nodosa, muscular dystrophies, dermatomyositis, and acute porphyria are other less common conditions which may have to be differentiated from polyneuritis.

### THERAPY

This must be largely symptomatic, since the etiology is so obscure. General nursing care—especially of those with marked weakness of the trunk and arms is vitally important. Feeding will be required when the arms are paralyzed and this must be carried out with great care in the presence of dysphagia. When the latter is pronounced it may be necessary to resort to intravenous fluids. A regular hospital diet is sufficient and there is no evidence to suggest that vitamins are in any way concerned with the development of or recovery from this condition.

Pain is best alleviated by salicylates, codeine, demerol, dilaudid or morphia, depending on its intensity. In some of the chronic painful types where sleep is interfered with the use of opiates is entirely justified. Hot packs give great relief in many cases.

Continued vigilance in the first two weeks should spot the early signs of respiratory embarrassment. This is one place where the Drinker respirator may be very helpful and any patient with this condition should be kept in close proximity to such a service. If it is needed it will be needed badly and quickly. A suction apparatus with which mucus can be aspirated from the pharynx should also be available. Any patient requiring a respirator is a potential case of pneumonia and penicillin should be given routinely during the early days of this part of the management.

Protective splints to prevent the stretching of weakened muscles should always be used. Foot-drop is the most important disability to be avoided. Physiotherapy in the form of massage, passive and later active exercise is of real help—particularly in the discouraged chronic patient.

Reassurance and encouragement are much needed in the care of this disease. The alarming complaint of dysphagia can be helped in this way, and fortunately its response to a soft diet plus reassurance is usually excellent. The assuring tone also neutralizes the apprehension that is so usual in the face of progressing respiratory difficulty. Encouragement should be dispensed generously to the patient who is often more or less totally helpless during the weeks and sometimes months that are taken up with a tedious convalescence.

## DISCUSSION OF CASES

Instead of going into an analysis of the 24 cases and the incidence of the various details met with, I am dividing them into four main groups. One or more typical cases will be reported under these different headings.

## THE FAVOURABLE GROUP

Guillain and Barré have described many patients with this syndrome and their names are often attached to it. They maintained that the outlook was always good.

### CASE 9

Male, aged 32. This man had a head cold on December 15, 1946. He felt quite well until the 18th when for no apparent reason he collapsed on the floor. He called a doctor on the 20th and was admitted to hospital. At this time he complained of some pain in the neck, back, arms and legs. Examination on the 21st showed facial diplegia, palatal weakness, dysphagia, dysphonia, marked weakness in the arms, chest muscles, trunk and legs. Respiration was accomplished with the aid of the accessory groups. The diaphragms were not involved. There was no sphincter disturbance. All the deep reflexes were lost. Sensory examination showed a decrease but not a loss of all modalities in a stocking-glove distribution. The cerebro-spinal fluid showed 167 mgm. of protein. The blood counts and sedimentation rate were normal. The temperature was normal. By the 27th swallowing was much easier and there was some return of power in the legs. On the 30th, twelve days after the onset of paralysis, the facial movements were improving, the strength in the hands was increasing, breathing was better and some flexion of the thighs was possible. At this time it was noted that the lower half of the abdominal musculature was weaker than the upper half, a not uncommon finding. On January 2nd, the movements in the ankles and hands were better but the arm groups were still very weak. The spinal fluid on this date showed no cells, 300 mgm. of protein and a flat gold curve. On January 13 he could rock himself into a sitting position, his hand grips were stronger, the chest expansion was returning, the lower abdominal weakness was no longer apparent, and the thighs could be flexed easily. By February 4 the chest excursion was much better, the trunk muscles allowed him to sit up easily, the power in the thighs was normal, sensory changes were no longer demonstrable, the knee jerks were just obtainable, and the spinal fluid protein was 90 mgm. From this day on he was up walking about the ward and he left the hospital fully recovered on the 13th—less than two months after the onset of his illness.

Treatment consisted of good nursing care, feeding during the period when the arms were paralyzed, a regular hospital diet without additional vitamins, and hot packs for the control of the pain in the back and limbs.

*Comment.*—This case exemplifies the Guillain-Barré syndrome in every respect—including the pleasing outcome. Once improvement began, it developed rapidly. The 10 cases in this group had all recovered completely within six months.

## CHRONIC POLYNEURITIS

In this group I have placed those patients who were still paralyzed at the end of six months. One characteristic case is detailed out of six observed.

### CASE 8

Female, aged 55. This patient was admitted to hospital in September 1945 with a history of having developed a fluctuating weakness of all four extremities during the previous year. She had been bed-ridden for several weeks before we saw her. For no apparent reason she had noted that the power would improve from time to time but never to anything like normal.

Physical examination showed a healthy and well-nourished appearance. There was a very marked proximal weakness in the arms and legs with about 90% loss of power in the hand grips and foot movements. The trunk muscles allowed her to retain the sitting position once she was placed in it. No cranial nerve changes or sphincter disturbances were present at that time. All the deep reflexes were absent. Vibration sense was lost below the knees. There was a marked peri-dental infection and pus could be expressed readily from the gums around four of her incisors. The spinal fluid showed no cells and 150 mgm. of protein. The patient was given general care with a full diet and vitamins in large quantities by mouth and by the intravenous route. The four infected teeth were removed. No improvement followed these measures.

In February 1946, after more than 14 months of increasing weakness in all four extremities to the point where she could not turn over in bed, sit up alone, feed herself, or write, she developed a severe attack of measles with a temperature of 102° for a period of four days. At the end of this period she found that she had a great increase in strength in the arms, hands, legs and trunk. For the first time in six months she was able to write a letter. She could sit up without help very easily. She could raise both legs straight up while lying on her back. Within a period of forty-eight hours she developed a remarkably complete range of movements in her fingers and toes. The hand grips were estimated at 30% of normal as compared with 10% before, and she wrote a four-page letter within a week of the time of the onset of the measles. The most marked improvement seemed to take place in the trunk and proximal muscle groups. There was of course no change in the deep reflexes. She had been seen by one of the orthopædic surgeons with a view to splinting in order to prevent foot-drop but it was felt that in view of the long progressive history of paralysis that such care was hardly indicated. Then to our great surprise she got out of bed and began moving about the ward in a walker—held up only by the foot-drop which had developed during the paralytic period. Within a week of the attack of measles she could stand on either foot and flex the opposite knee. She walked out of the hospital without assistance on March 15, six weeks after the occurrence of the measles.

Without history of infection or any other illness she was re-admitted in a state of complete paralysis on April 17. In addition there was marked dysphagia associated with choking spells. The spinal fluid protein was 250 mgm. Because of the improvement which followed her febrile period with the measles we felt that the use of typhoid vaccine might accomplish the same effect. This was tried in the form of single and then continuous injections. Seven hundred and fifty million organisms in 1,000 c.c. normal saline at a rate of 20 drops per minute intravenously gave an elevation of temperature to between 102 and 104° for a period of ten hours. Improvement in power was striking—she could raise her arms freely and sit up without support. However it never equalled the gain which followed the attack of measles, and she developed such a marked circulatory reaction with the fourth treatment that we had to abandon the idea. One week later she had intestinal "flu" and after that there was never any period of significant increase in muscle power until her discharge in November, 1946.

Examination in November, 1947, three years after the beginning of her illness, shows a very healthy appearance, no evidence of muscle wasting, and the same picture of flaccid paralysis and a-reflexia.

*Comment.*—This case emphasizes the chronicity that we may encounter in polyneuritis. It points to our helplessness in altering the course of this disease. All of our so-called chronic cases have begun insidiously without history of previous infection. The future for such patients is not necessarily dark and three of the six recovered completely. In the early phases of this type of the disease the patient is sometimes called a neurotic until the reflexes and spinal fluid are checked. The paralysis often develops slowly with remissions and exacerbations. Fever induced by the intravenous use of typhoid vaccine is not of any therapeutic value. Cases of polyneuritis have followed the use of the fever cabinet in the therapy of other conditions.

## PAINFUL TYPES

Two of three case histories are submitted as examples of this variant. In all three cases the pain overshadowed the muscular weakness for several weeks before the correct diagnosis was made. The youngest patient was thought to have arthritis and the two women of 59 and 78 years were first investigated as probable examples of metastatic malignancy in the spine.

### CASE 6

Female, aged 59. After having a low-grade respiratory infection for several weeks during the spring this patient was admitted to hospital in June, 1946. She complained of tingling sensations in the hands and areas of intense hyperæsthesia over the left forearm, the right shin and the extensor surface of the left foot and lower calf. The feet were cold. Stabbing pain in the left buttock developed. Vomiting was a troublesome feature which was not evidently related to the pain. She had lost 15 pounds in weight in the first month and continued to lose weight in hosiptal.

Physical examination showed weakness in the arms and legs which increased steadily. The deep reflexes were all absent. There were no bulbar or sphincter changes. The spinal fluid showed no cells but 110 and then 90 mgm. of protein. During the three months following admission the control of pain was very difficult and as a result of remaining in one position most of the time she developed arthritic changes in the left shoulder and stiffness of the fingers. The sedimentation rate ranged from 54 to 106 mm. in one hour. The electrocardiogram was normal. X-rays of the chest, pelvis, skull and colon were all normal. There was no fever during the hospital period.

Management consisted of general nursing care and pantopon 1 c.c. as needed for pain (this was not very satisfactory). Towards the end of her stay in hospital she was up in a chair and eating well. She had a lot of pain in the left shoulder and the tips of her fingers were tender. The muscle power in the legs was returning steadily when she was discharged twelve weeks after admission on September 12. On December 7 she came back with excruciating pain—so severe that she could scarcely be moved—in the back, arms, groins, and legs. Dilaudid gr. 1/32 afforded very little relief. The legs were found to be completely paralyzed but when they were moved passively the pain was intense. Paralysis of bowel and bladder function was noted for the first time. The power in the arms was not affected. The spinal fluid showed no cells but 150 mgm. of protein.

The bladder became infected and pus was present in the urine throughout the remainder of the illness. In spite of the total paralysis in the legs the patient continued to have extreme pain in the legs, and also in the back, abdomen, and the right arm. By December 15 leg pain continued to be her chief complaint.

There was anæsthesia to pin prick below the 9th dorsal level on the left and the mid-thigh level on the right. Pain alternated between the right and left legs at this stage of her illness and was almost uncontrollable. By December 22, bed sores had appeared. Frequent liquid bowel movements were passed involuntarily. At times the patient was irrational. She cried a great deal of the time and it was necessary to give her dilaudid every four to six hours. At this time we did not feel that there was any chance of survival and we felt quite justified in this course. During this phase the calf muscles were sensitive to pressure. In desperation we tried intravenous typhoid vaccine in the hope of improving the patient's condition. Following an elevation of temperature to 106 the patient seemed to show marked improvement but it was short-lived and within a week she was just as bad as before the injection of vaccine. By January 27 she was having a lot of pain in the shoulders and elbows but the pain in the lower half of the body had almost disappeared and she was moving her left foot and leg freely. Hypodermics were unnecessary by February 16. She began sitting on the edge of the bed, and she was up in a chair by March 10. On March 26 the pain in the left arm had increased to a point were she was crying with it. There was associated interscapular pain and pains in the legs were beginning to return. On April 8 she developed pain in the eyes. By April 12 the right eye was blind and vision in the left eye was reduced to perception of moving objects. At this time the nerve heads appeared blurred and congested but there was no measurable papillœdema. The spinal fluid at this time showed no cells but the protein was increased to 210 mgm. After this, pains in the arms became very intense and dysphagia appeared. She ran a progressive down-hill course and died on June 2.

A post-mortem by Dr. John Fisher showed polyneuritis; necrotizing cystitis; acute pyelonephritis (left); atrophy of viscera (heart, lymphoid tissue, adrenal cortex); chronic passive congestion of liver and spleen; pulmonary atelectasis (left).

*Weigert stains of spinal cord, optic nerves and spinal nerve roots.*—In the spinal cord degeneration is most marked in the dorsal columns. Of these the column of Goll is more severely involved but at some levels almost the entire dorsal columns have degenerated. Not only have they lost their myelin sheaths but there is actual disintegration of nerve fibres and accumulations of microglia scavenger cells. In addition at one level the ventral columns are quite severely degenerated and to a mild degree the lateral columns are also involved. In the latter there is some vacuolation and patchy myelin sheath degeneration but it is not a pronounced change. The grey matter at all levels is uninvolved. The optic nerves show a very severe degeneration. Not only is there marked fragmentation and loss of myelin sheaths but there is also actual disintegration of the axis cylinders and accumulations of numerous microglia scavenger cells. The spinal ganglia show marked fragmentation and degeneration of myelin sheaths with a general shrinkage of the posterior nerve roots. Many of the ganglion cells themselves have lost their nuclei and are ragged and disintegrating.

*Comment.*—This case followed a course in which pain was the dominant clinical feature. The flaccid paralysis with a-reflexia and the high spinal fluid protein throughout the illness placed her in the polyneuritis group. It seems to illustrate how so-called peripheral neuritis may

merge into serious central nervous system disease with permanent myelitis and optic nerve changes.

CASE 5

Male, aged 25. Following a bronchial cold towards the end of March, 1947, this patient complained of numbness and then pain in the toes, insteps, and above the ankles. It was described as a cutting or pulling type of pain which prevented sleep, and it had resulted in a drop in weight from 175 to an estimated 100 pounds by the time he was admitted to hospital on May 26. Morphia did not relieve the pain adequately. For three weeks prior to his hospital study there had been profuse sweating of both feet.

Examination showed the under-nutrition, well-marked weakness of peripheral type in all four extremities, loss of all of the deep reflexes, no sensory loss, no muscle tenderness, palms and soles which were constantly red and bathed in perspiration, exquisite tenderness of the soles of the feet when handled in any way, a normal temperature and blood picture, and a spinal fluid without cells but with 430 mgm. of protein and a mid-zone curve.

Examined again in November, he was up to 150 pounds in weight. The power in the upper limbs was normal but the palms were still cold, red and wet. The legs and feet were strong but the soles were so tender that he could not stand comfortably. The feet were reddened, cold and very moist. All the deep reflexes were still absent. The spinal fluid protein was 40 mgm. By March, 1948, he had completely recovered and had returned to work.

*Comment.*—This man had a symmetrical weakness, a-reflexia, and a high spinal fluid protein. In addition there was much evidence of a serious disturbance in the sympathetic connections with the extremities. Eight months after the muscle power had returned to normal the pain continued to a point where he could not walk. It finally disappeared completely eleven months after the onset of the illness.

THE CRITICAL GROUP

These five patients ran a more rapid course than the others and respiratory or bulbar involvement developed within the first two weeks in four and within a month in the fifth. Two histories are given.

CASE 1

Female, aged 32. This healthy farm woman did a washing on Friday August 10, 1945, and that night experienced numbness in her toes and a general restlessness. The next day she went to see her doctor with these two complaints. On Sunday she had tingling sensations in the fingers of the left hand. On Monday both legs were weak and unsteady. She was admitted to the hospital on Tuesday at which time she could not feed herself and was having difficulty in swallowing. She complained of pains in the hips, legs, back, shoulders and arms. Her voice was thick, she was restless, and very apprehensive.

Physical examination showed a symmetrical flaccid paralysis of all four extremities, the trunk muscles, and the muscles concerned with micturition. The ankle jerks were absent but the knee jerks were both active. There was no sensory loss and no hypæsthesia. The next day the knee jerks had both vanished. The diaphragms on clinical examination appeared to be active. The mouth showed a marked gingivitis with pyorrhœa. The spinal fluid pressure was normal, there were no cells, and 60 mgm. of protein. The Hgb. was 74%; red blood cells 3,620,000, and white blood cells 10,000. The sedimentation rate was 58 mm. in one hour. Four days following admission she showed facial diplegia. That afternoon she developed respiratory embarrassment. She was placed in the Drinker respirator and seemed to respond well. The throat was kept clear of mucus. In addition to general nursing care she was given penicillin, 30,000 units q. 3 h., intravenous glucose, small doses of morphine and hyoscine for the control of her restlessness, and she was catheterized every twelve hours. The next day her temperature was 99°, the pulse was 128 and the respirations 32. She became very cyanosed when she was removed from the respirator. Mucus in the throat was troublesome and she was unable to swallow. The restlessness became more marked and she showed mental confuson. The temperature rose to 104, the pulse to 148, the respirations to 36, and she expired.

CASE 2

Male, aged 32. This man had had a throat infection followed by cough and pleurisy in August, 1942 before he was admitted to the hospital. On examination the psyche was clear. He had difficulty in talking, protruding the tongue, and in swallowing. The legs were totally paralyzed. The arm muscles showed extreme weakness and they were tender on palpation. There was marked respiratory difficulty and on clinical examination the diaphragms appeared to be inactive. He had a lot of trouble expelling mucus. There was weakness of the left side of the face and the tongue protruded to the left. All the deep reflexes were absent. The pulse rate was 140, the temperature 101° and the respiratory rate 26. The spinal fluid showed five cells, the protein level was not estimated but the gold curve showed a first-zone elevation. The patient appeared critically ill and he was placed in the Drinker respirator with the head lowered to facilitate aspiration of mucus from the throat. He became irrational and was cyanosed at times. Pains in the limbs were complained of frequently. Because of dysphagia he was carried along for a month on intravenous fluids, sips of milk and fruit juices by mouth, and intramuscular vitamins. During this period he was confused a good part of the time and was involuntary. He began to improve slowly but required the respirator on and off for two and a half months. Convalescence was greatly prolonged but continued to be steady and he was able to return to work one year after the onset of his illness.

*Comment.*—These cases show the difficulty of trying to make a prognosis too early in this disease. They suggest that the respirator may save an occasional patient but (as noted by several writers) that death when it comes is associated with involvement of the bulbar area or its connections and not only of the nerve paths to the respiratory muscles.

SUMMARY

Infectious polyneuritis is a definite entity with motor weakness, pain which is sometimes severe, and occasionally autonomic disturbances. Its diagnosis is strengthened by the finding of a spinal fluid with an increased protein in the absence of cells.

It is predominantly peripheral in distribution but there may be associated involvement of the central nervous system at any level.

It carries a significant mortality (37% in this series of 24 patients) and the course is often prolonged indefinitely in spite of various therapeutic measures.

There is no evidence to suggest that vitamins have any important place in the etiology or therapy of this syndrome.

An obvious focus of infection should be removed in order to improve the general condition of the patient. Such removal is not likely to shorten the course of the polyneuritis appreciably.

Fever therapy does not have any place in the management of this disease. Its use in other conditions has been followed by polyneuritis.

Cases representing favourable outcome, painful syndromes, chronic courses, and the most serious side of this condition are submitted.

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Waterloo at Picadilly.

## THE QUESTIONABLE IMPORTANCE OF BLOOD CHANGES IN CORONARY OCCLUSION*

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THIS is a report of the results of blood studies on 31 patients with acute coronary thrombosis, 15 of which were the subject of a preliminary report.[1] Changes observed in the Waugh-Ruddick test, prothrombin time, coagulation time, circulation time, blood volume, hæmatocrit and plasma proteins are reported on a total of 31 cases of acute coronary occlusion admitted to the medical wards of the Montreal General Hospital from January 28, 1946, to June 30, 1947. Results of the use of dicoumarol in the treatment of these cases will be made the subject of a later paper as the study of this method of therapy is still proceeding.

Alternate patients admitted to the medical wards received dicoumarol therapy. A total of 15 patients were treated with this anticoagulant and 16 patients were used as controls but all cases were otherwise given similar supportive therapy.

Blood studies were carried out on all patients shortly after admission and were repeated weekly thereafter with the exception of the blood volume determinations. This latter test was done immediately after admission on 19 patients and repeated before discharge from hospital in 12. The prothrombin time was carried out every second day in the dicoumarol-treated patients, or daily if necessary to control the dosage.

*The Waugh-Ruddick test.*—This procedure has been described in detail in a previous paper.[1] Briefly it consists of measuring the anticoagulant effect of serial dilutions of heparin on blood *in vitro*. By slowing down the coagulation of blood the originators of this test hoped to be able to measure small changes in increased or decreased coagulability. Seven dilutions of heparin were used, beginning at 0.05 up to 0.35 units of heparin per ½ c.c. of 0.9% NaCl. 1 c.c. of blood was added to each dilution of heparin as well as to two control tubes, one dry and one containing ½ c.c. of saline. The coagulation time for each tube was plotted and a heparin dilution-time curve obtained.

*Results of Waugh-Ruddick test.*—One hundred and thirty-eight tests were carried out on the 31 patients. In 61 of these tests the curves were irregular. This high percentage of irregular curves was noted in our previous paper and has continued to make its appearance in the additional 16 patients studied since the initial report. Table I shows the results of the Waugh-Ruddick test on admission and its subsequent course during hospitalization in 14 controls and 15 dicoumarol treated patients. It will be noted that of the 31 cases tested on admission, the test was within normal limits in 20 (or 64.5%), that is, blood coagulability was normal as measured by the test. In 6 cases (19.4%) the curves were low, indicating an increased tendency to clot while in 5 cases (16.1%) the curves were high indicating a decreased tendency to clot.

During hospitalization, 9 of the 14 cases who did not receive dicoumarol showed no change in blood coagulability. Two cases showed an increased tendency to clot while in 3 cases the tendency to clot became less marked.

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In the 15 cases treated with dicoumarol 8 showed a decreased tendency to clot during hospitalization and treatment, 5 had no alteration in clotting tendency and 2 actually showed an increased coagulability. The latter two cases were resistant to dicoumarol and were difficult to maintain at a satisfactory prothrombin level.

From these results it will be seen that normal or decreased coagulability of the blood was found on admission in 77.4% of cases of acute coronary thrombosis. In only 22.6% (7 cases) was there an indication of an increased clotting tendency. These findings are at variance with those of Ogura *et al.*[2]

TABLE I.
WAUGH-RUDDICK TEST ON ADMISSION

| *Admission value* | *No. of cases* |
|---|---|
| Normal | 20 |
| High | 5 |
| Low | 6 |
| Total | 31 |

COURSE OF WAUGH-RUDDICK TEST DURING HOSPITALIZATION IN 14 CONTROLS

| *Admission value* | *No. of cases* | *Unchanged* | *Rose* | *Fell* |
|---|---|---|---|---|
| Normal | 9 | 7 | 1 | 1 |
| High | 1 | 0 | 0 | 1 |
| Low | 4 | 2 | 2 | 0 |

COURSE OF WAUGH-RUDDICK TEST DURING HOSPITALIZATION IN 15 TREATED CASES

| *Admission value* | *No. of cases* | *Unchanged* | *Rose* | *Fell* |
|---|---|---|---|---|
| Normal | 9 | 2 | 6 | 1 |
| High | 4 | 2 | 1 | 1 |
| Low | 2 | 1 | 1 | 0 |

Of the 14 cases under strict bed rest not receiving dicoumarol only 2 showed an increased clotting tendency during hospitalization. In the majority (9 cases) coagulability of the blood remained unchanged, while in three cases, the coagulability decreased.

The above findings confirm our previously expressed view that the Waugh-Ruddick test is not abnormal in a significant percentage of individuals suffering from acute coronary occlusion.

*The prothrombin time.* — The prothrombin time was determined by Quick's method[3] using thromboplastin prepared weekly from the brain of a freshly killed rabbit. In 22 of the 31 cases, prothrombin times on undiluted plasma were compared with those obtained on plasma diluted 1:8 with normal saline. It has been claimed,[4, 7] that by such dilution smaller variations in prothrombin content can be measured. Shapiro[4] believes that dilution of the plasma renders certain naturally occurring anti-coagulants ineffective. In the preliminary report it was suggested that the prothrombin time using diluted plasma is not a reliable guide in the dosage of dicoumarol because of the great variability of the results obtained by this method, especially when the prothrombin time is prolonged.

TABLE II.
PROTHROMBIN TIME AND COAGULATION TIME ON ADMISSION

| *Case* | *Prothrombin time in seconds diluted plasma* | *Whole plasma* | *Coagulation time in minutes* |
|---|---|---|---|
| 1 | ..... | 15.0″ | 10.0′ |
| 2 | 67.5″ | 16.25″ | 13.0′ |
| 3 | ..... | 17.0″ | 12.0′ |
| 4 | 230.0″ | 30.0″ | 13.0′ |
| 5 | ..... | 17.0″ | 10.0′ |
| 6 | 74.0″ | 15.0″ | 9.0′ |
| 7 | 72.0″ | 15.0″ | 16.0′ |
| 8 | ..... | 13.5″ | 11.5′ |
| 9 | ..... | 15.0″ | 14.0′ |
| 10 | ..... | 16.0″ | 15.0′ |
| 11 | 66.0″ | 13.5″ | 15.0′ |
| 12 | ..... | 17.0″ | 11.0′ |
| 13 | ..... | 17.0″ | 12.0′ |
| 14 | 191.0″ | 20.5″ | 18.0′ |
| 15 | 61.0″ | 15.0″ | 13.0′ |
| 16 | 72.0″ | 18.0″ | 16.0′ |
| 17 | 76.0″ | 16.0″ | 10.5′ |
| 18 | 70.0″ | 20.5″ | 16.0′ |
| 19 | 63.0″ | 21.0″ | 12.0′ |
| 20 | 60.5″ | 17.5″ | 18.0′ |
| 21 | 80.0″ | 16.0″ | 15.0′ |
| 22 | 75.0″ | 16.0″ | 20.0′ |
| 23 | 60.0″ | 16.5″ | 10.0′ |
| 24 | ..... | 15.0″ | 14.5′ |
| 25 | 72.0″ | 18.0″ | 9.5′ |
| 26 | 42.0″ | 13.0″ | 19.0′ |
| 27 | 55.0″ | 16.0″ | 11.0′ |
| 28 | 50.0″ | 17.5″ | 13.5′ |
| 29 | 80.0″ | 15.5″ | 10.0′ |
| 30 | 63.0″ | 20.0″ | 11.0′ |
| 31 | 46.0″ | 14.0″ | 11.0′ |

No. of cases with prothrombin times below normal: whole plasma 4; diluted plasma 4; total 6 (*i.e.* 2 cases were below normal in both whole and dilute plasma.)

No. of cases with prothrombin times at lower limit of normal: whole plasma 14; diluted plasma 7; total 17 (*i.e.*, overlap of 4 cases.)

Table II records the prothrombin times and coagulation times on admission. Normal prothrombin time was taken as 15 to 22 seconds for whole plasma, and 60 to 80 seconds for dilute (12.5%) plasma. It will be noted that four patients showed decreased prothrombin times when whole plasma was used. Two of these same cases showed decreased prothrombin times when diluted plasma was used. However, two

further cases showed decreased prothrombin times only when diluted plasma was used.

An additional 17 cases showed prothrombin time values nearing the lower limit of normal by one or other method but in only four of these cases was there complete agreement between the two methods. Increased prothrombin times were found in 2 cases, and in only one of these were both the dilute and the whole plasma prothrombin times elevated. In another of the 2 cases, the dilute plasma prothrombin time was 191 seconds, despite a normal whole plasma prothrombin time of 20.5 seconds.

These results are essentially in agreement with those published in our earlier report. They support the work of Cotlove and Vorzimer,[5] and Wright[6] and are at variance with reports by Peters,[7] Meyers and Poindexter[8] and Doles.[9] It would appear that no constant lowering in prothrombin time is present on admission in cases of acute coronary thrombosis.

In 13 control cases who did not receive dicoumarol, prothrombin times were done weekly. The group included 3 of the 6 cases found to have a shortened prothrombin time on admission and 1 case with an elevated admission prothrombin time (30″ undiluted plasma). All the cases which were normal on admission remained normal. The prothrombin times of all 3 cases low on admission rose to normal, one of the three falling later. The values in one case with an initial elevated prothrombin time fell towards normal but remained at 24″ (whole plasma).

It is interesting to note that of the 4 fatal cases 3 had low normal prothrombin times but one maintained a definitely elevated prothrombin time (diluted plasma) although the whole plasma prothrombin time was 20.5 seconds at the time of admission to hospital.

In view of the above findings it does not seem that hyperprothrombinæmia or hypoprothrombinæmia is a constant accompaniment of acute coronary thrombosis. It would appear that there is no constant disturbance of this factor in the clotting mechanism.

*Clotting time.*—The three-tube method of Lee and White was used to measure the clotting time. Results of the admission values are to be found in Table II. The normal range is considered to be 10 to 15 minutes. Only two cases had a value on admission below the lower limits of normal. No constant variation in clotting time was found

TABLE III.
CIRCULATION TIME

| *Case* | *Time (admission)* | *Behaviour* | *Cardiac failure on admission* | *Clinical shock on admission* | *Clinical course* |
|---|---|---|---|---|---|
| 1 | 19.0″ | Unchanged (18 to 20″) | Sl. left | No | Recovered |
| 2 | 20.0″ | One determination | Sl. “ | No | Left hospital against advice |
| 3 | 15.0″ | Varied (12½ to 15″) | No | No | Recovered |
| 4 | 27.0″ | Rose (47″) | No | Mild | “ |
| 5 | 27.5″ | Fell (16 to 20″) | No | No | “ |
| 6 | 32.0″ | Fell (14 to 27″) | No | No | “ |
| 7 | 17.0″ | Unchanged | No | Yes | “ |
| 8 | 18.0″ | Varied (18 to 23½″) | No | No | “ |
| 9 | 21.0″ | Unchanged | No | Mild | “ |
| 10 | 16.0″ | Unchanged | Sl. left | No | “ |
| 11 | 28.0″ | Unchanged | Sl. “ | No | “ |
| 12 | No response | Fell (29 to 20″) | Sl. “ | Yes | “ |
| 13 | 30.0″ | Varied (22 to 35″) | Sl. “ | Yes | “ |
| 14 | 28.0″ | One determination | Yes | Yes | Died |
| 15 | 19.0″ | One determination | No | No | “ |
| 16 | 22½″ | Varied (19½ to 30″) | No | Yes | Recovered |
| 17 | 21½″ | Rose (24″) | Left | Yes | Died |
| 18 | 14½″ | Varied (15 to 17″) | No | No | Recovered |
| 19 | | 25″ (One determination) | Sl. left | No | Died |
| 20 | 30.0″ | Fell (15 to 20″) | Sl. “ | Mild | Recovered |
| 21 | 20.0″ | Unchanged | No | No | “ |
| 22 | 30.0″ | Fell (20 to 29″) | No | Yes | “ |
| 23 | 20.0″ | Unchanged<br>Rose to 38″ | No | No | “ |
| 24 | 30.0″ | Fell to 23″ | Right | Yes | Recovered |
| 25 | 23.0″ | Rose to 32″ | Right | No | “ |
| 26 | 25.0″ | Fell to 19″ | No | Yes | “ |
| 27 | 21.0″ | Fell to 15″ | No | No | “ |
| 28 | 15.0″ | Rose to 25″ | No | No | “ |
| 29 | 30.0″ | Fell to 23″ | Left | No | “ |
| 30 | 25.0″ | One determination | No | Mild | Died |
| 31 | 25.0″ | Fell to 15″ | Mild | No | Recovered |

during hospitalization in 13 patients who were not receiving dicoumarol. The patients treated with this drug tended to show a slightly prolonged clotting time, while under anti-coagulant therapy. In one case the clotting time rose to 30 minutes on one occasion.

*Circulation time.*—The intravenous Decholin arm to tongue circulation time was used in this study (normal 15 to 20 seconds). The results obtained are found in Table III. In this table the values obtained on admission are given along with the subsequent changes which occurred during hospitalization in each case. These findings are correlated with the presence or absence of clinical shock and cardiac failure on admission and also with the clinical course of the patients. It will be noted that in 14 of the 31 patients the admission circulation times were 23 seconds or over. The longest time obtained was 32 seconds; 4 additional cases had values above 20 and under 23″. The remaining 13 patients had normal admission values. Of the 18 cases with prolonged circulation times on admission, (14 cases 23″ and over and 4 cases above 20 and under 23″) 8 fell during hospitalization to values nearer normal; 2 rose and remained elevated; 2 had one determination only; 5 remained unchanged and 1 fell but rose again. In addition to these 18 cases 2 had an unsatisfactory test on admission, but when the tests were repeated 1 week later they were found to be elevated. In one of these patients the value subsequently fell to normal, but in the other only one determination was carried out.

Of the 14 cases with definitely prolonged admission circulation times 8 showed some degree of clinical shock. Eight of the 14 had evidence of cardiac failure and in 4, shock and cardiac failure coexisted. Only 2 cases did not show clinical evidence of shock or cardiac failure. It is interesting that in 4 cases clinical shock was present with a normal circulation time and in 4 cases some degree of cardiac failure was present with circulation time values below 23 seconds.

Correlating these values with the clinical course of the disease reveals the fact that of the 4 patients who died 2 had elevated circulation times on admission, 1 had a borderline value (21½″) which rose prior to death to 24″. The 4th case had a circulation time at the upper limit of normal but died before it could be repeated.

From these figures it will be seen that over half these patients suffering from acute coronary occlusion had a prolonged circulation time on admission to hospital (18 out of 31 cases). In the majority of these, either some degree of cardiac failure or clinical shock or both was present. The circulation time then would appear to bear a relationship to the efficiency of the circulation as a whole and to a certain extent to the functional ability of the heart. These findings tend to corroborate those of Selzer[10] who found in a study of the circulation times in 45 cases of acute coronary thrombosis with infarction that in the early stages there is a prolongation of the circulation time which returns towards normal with healing of the infarct. He ascribes this slowing of the circulation to myocardial inefficiency. It appears from our results that the presence of shock itself may have an influence on this test. It will be seen that the finding of a slowed circulation time in cases such as these does not necessarily mean a poor prognosis but it is interesting to note that only one of the four cases who died had a normal circulation time on admission.

TABLE IV.

BLOOD VOLUME IN 12 CASES WHERE TEST REPEATED

| *Case* | *Admission val. (c.c.)* | *Course* | *Discharge val. (c.c.)* | *Shock on admission* | *Circulation failure on admission* |
|---|---|---|---|---|---|
| 8 | 3507 | Rose | 4543 | No | No |
| 10 | 6702 | Unchanged | 6980 | No | Slight left |
| 12 | 6238 | Fell | 4360 | Yes | Slight left |
| 13 | 5665 | Fell | 4195 | Yes | Slight left |
| 16 | 5145 | Rose | 6104 | Yes | No |
| 18 | 6580 | Fell | 5575 | No | No |
| 20 | 6677 | Rose | 7160 | Yes (slight) | Slight left |
| 23 | 5208 | Fell | 3753 | No | No |
| 25 | 4535 | Rose | 6420 | No | Right |
| 27 | 4450 | Rose | 5003 | No | No |
| 28 | 4732 | Unchanged | 5021 | No | No |
| 31 | 3967 | Unchanged | 4300 | Yes | Left |

*Blood volume.*—The plasma and blood volumes were estimated on admission in 19 patients and repeated prior to discharge in 12. The Evans Blue method using a photo-electric colorimeter was employed. The results obtained in those cases where the test was repeated are to be found in Table IV. It will be seen that in 5 cases the blood volume rose during hospitalization, in 4 cases it fell, while in the remaining 3 cases the values were unchanged. It is unfortunate that in none of the cases who died was the blood volume repeated prior to death. Discussion of these results is deferred until the findings for the hæmatocrit and plasma protein values have been recorded.

TABLE V.
HÆMATOCRIT

| Case | Admission value | Course | Shock |
|---|---|---|---|
| | % | | |
| 1 | 50.0 | Fell (44 to 46.5%) | No |
| 2 | 46.0 | One determination | No |
| 3 | 46.0 | Unchanged (45 to 48%) | No |
| 4 | 40.0 | Unchanged | Mild |
| 5 | 56.5 | Fell (43 to 49%) | No |
| 6 | 48.0 | Unchanged | No |
| 7 | 52.5 | Fell (41.5 to 46.5%) | Yes |
| 8 | 39.5 | Fell (34.5%) | No |
| 9 | 59.5 | Varied (56.5 to 63%) | Mild |
| 10 | 58.0 | Fell (48 to 53%) | No |
| 11 | 47.5 | Unchanged (43.5%) | No |
| 12 | 45.5 | Unchanged (47 to 49.5%) | Yes |
| 13 | 45.0 | Varied to 40% then rose to 45% | Yes |
| 14 | 40.0 | One determination (died) | Yes |
| 15 | 44.5 | One determination (died) | No |
| 16 | 54.0 | Fell (45 to 50%) | Yes |
| 17 | 48.0 | Unchanged (46.5%) | Yes |
| 18 | 53.0 | Varied (47.5 to 52%) | No |
| 19 | 37.5 | Rose (45%) | No |
| 20 | 52.0 | Varied (47.3 to 53%) | Mild |
| 21 | 53.5 | Fell (46.5 to 48%) | No |
| 22 | 46.5 | Fell (37.5 to 40%) | Yes |
| 23 | 50.0 | Fell (44.5%) | No |
| 24 | 43.5 | Fell (36.5 to 38%) | Yes |
| 25 | 44.0 | Unchanged | No |
| 26 | 43.0 | Unchanged (46.5%) | Yes |
| 27 | 47.0 | Fell (42 to 43.5%) | No |
| 28 | 37.5 | Unchanged | No |
| 29 | 52.0 | Fell (47.5%) | No |
| 30 | 41.0 | Unchanged (died) | No |
| 31 | 47.5 | Varied (47.5 to 50%) | No |

*Hæmatocrit values.* — Hæmatocrit estimations using a Wintrobe hæmatocrit and centrifuging at 2,800 r.p.m. for 30 minutes were done weekly on all patients. Results are to be found in Table V. A fall in cell volume of 5% or over was found in 12 of the 28 cases in which the test was repeated. A rise was observed in 1 while 10 remained unchanged and 5 varied in an inconstant manner. It will be noted that clinical shock was present in 4 of the cases showing a drop in cell volume but was present in 8 other instances where no such change took place.

*Plasma proteins.*—The plasma proteins were determined by the copper sulphate method.[11] In all but one case the findings were within normal limits and only minor variations occurred during hospitalization. In one case a value of 5.58 gm. % was obtained on admission but this subsequently rose to 6.50 gm. % during hospitalization.

*Discussion and interpretation of the blood volume and hæmatocrit findings.*—Table VI has been prepared to correlate the blood volume and hæmatocrit studies with the clinical findings of shock and cardiac failure in the 12 cases in which the blood volume studies were repeated. In clinical shock the volume of the circulating blood may be decreased.[15, 16] In congestive failure on the other hand, Gibson,[12] and de Palma and Kendall,[13] have shown that the total circulating blood is increased. They believe that this finding is most marked in severe cases and tends to return towards normal as this condition improves. In our 12 cases (Table VI), 6 had some degree of cardiac failure on admission as shown by the clinical findings, while 5 cases were in shock. In 4 of these cases the two con-

TABLE VI.
CORRELATION OF BLOOD VOLUME STUDIES AND CLINICAL FINDINGS

| Case No. | Blood volume | Hæmatocrit | Plasma protein | Clinical shock on admission | Cardiac failure on admission |
|---|---|---|---|---|---|
| 8 | Rose | Fell | Varied | No | No |
| 10 | Unchanged | Fell | Unchanged | No | Slight left-sided |
| 12 | Fell | Rose | Unchanged | Yes | Yes |
| 13 | Fell | Fell then rose again | Unchanged | Yes | Yes |
| 16 | Rose | Fell | Fell | Yes | No |
| 18 | Fell | Varied | Fell | No | No |
| 20 | Unchanged | Varied | Unchanged | Yes | Slight left-sided |
| 23 | Fell | Fell | Rose | No | No |
| 25 | Rose | Unchanged | Rose | No | Yes |
| 27 | Rose | Fell | Varied | No | No |
| 28 | Unchanged | Unchanged | Unchanged | No | No |
| 31 | Unchanged | Varied | Varied | Yes | Yes |

ditions co-existed. On the basis of the above observations it would be expected that the behaviour of the blood volume and hæmatocrit would be influenced in opposite directions by these two clinical states and the final result would be due to the balance between them. In the 4 cases where both shock and cardiac failure were present, the blood volume fell in 2 with a concomitant rise in hæmatocrit. In the other two cases, the blood volume remained unchanged, the cell volume remaining unchanged in one of these and varying in the other. In the one case showing shock unaccompanied by clinical evidence of cardiac failure the blood volume rose while the hæmatocrit reading fell. In the one case where there was cardiac failure and no shock the blood volume again rose somewhat but the hæmatocrit remained unchanged. This patient showed very marked right-sided cardiac failure, the rise in blood volume coinciding with a deterioration in his clinical state. In 2 cases where no shock or failure existed clinically the blood volume rose while the hæmatocrit values fell, indicating that the conditions found in shock were present but were not clinically manifest. In 2 cases also without clinical evidence of shock or failure the blood volume fell. In one of these the hæmatocrit values fell and in the other they varied. These results may be attributed either to subclinical cardiac failure or the effect of bed rest alone (Taylor and Erickson[14]).

### SUMMARY AND CONCLUSIONS

1. No constant changes in blood coagulability as measured by the Waugh-Ruddick test, plasma prothrombin time or coagulation time were noted in 31 cases of acute coronary thrombosis. No constant changes in the Waugh-Ruddick test resulted from prolonged bed rest in the cases studied.

2. No constant variation was observed in plasma protein levels during convalescence.

3. A high percentage of patients suffering from acute coronary thrombosis have prolonged circulation times, due either to shock or to myocardial weakness, or to a combination of these factors.

4. The results of blood volume studies in these cases support the view widely held that the values vary with the presence or absence of cardiac failure and/or clinical shock.

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## STUDIES IN PROGRESSIVE LIPODYSTROPHY*

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IN 1885, Weir Mitchell described to the Philadelphia Neurological Society a "Singular Case of Absence of Adipose Matter" in the upper half of the body of a twelve year old girl. This curious condition followed an attack of severe cold with cough and expectoration which lasted for three months at the age of five years.[1] Ten years later a similar patient was observed by Osler: he noted the sharp contrast between the extremely emaciated face and trunk and fairly plump lower part of the body in a ten year old girl. The wasting had begun at five years of age. This case did not appear in the literature at that time but was subsequently reported by Weber.[2] The disease was not recognized as a clinical entity, however, until Barraquer in Barcelona[3] and a year later, Campbell in England[4] published their studies in this curious condition. Other cases have been reported[5, 6] since that time, but the first detailed study of this disease was made by Simons[7] who named it lipodystrophy progressiva. It is also known as Barraquer-Simons disease, lipodystrophy progressiva superior, and craniothoraco lipodystrophy.

By 1940 about one hundred cases were reported from different parts of the world[10] but

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many more must have remained unrecognized since the disease is self-arresting.

*Onset and course.*—Progressive lipodystrophy is more common among females and is characterized by gradual disappearance of subcutaneous fat usually first from the face, then affecting the neck, shoulders, arms and trunk. In some cases (more common among men) the atrophy is confined to the face and neck alone.[11] In females there frequently is a considerable increase of subcutaneous fat in the lower half of the body. In a few cases the conspicuous enlargement of the buttocks and thighs was reported to precede the loss of fat from the upper part of the body. Thus the disease may combine both the *atrophic* and *hypertrophic* features at once.

The onset of this condition is usually quite insidious. The loss of subcutaneous tissue becomes apparent as a bilateral symmetrical thinning of the face occurring before puberty, frequently in the first decade of life. No obvious disturbances of glandular activity are present. Some authors reported the presence of menstrual irregularity and even sterility in females; however, many of the female patients having progressive lipodystrophy had married and given birth to normal children. Usually the loss of subcutaneous fat spreads from the neck to the shoulders, arms and then trunk. This feature is responsible for the term "progressive" but the progress of the disease ordinarily comes to a spontaneous arrest when the subcutaneous fat has disappeared from the upper part of the body.

Although the patient may have some vague complaints during the "active" period associated with the loss of subcutaneous fat, no specific symptoms have been found and all systems are apparently normal. By the time the progressive feature of the disease has run its course, thin skin alone covers the bony framework and the muscles. The typical appearance of such an individual is characterized by deep-set eyes, prominent malar bones, hollowed temples and cheeks and the whole face is deeply furrowed. The neck is usually thin and stringy and the thorax is bony, with prominent clavicles, scapulæ and vertebræ. The breasts in the female are usually small and pendulous, the muscles are clearly defined and appear to be over-developed, the abdomen is thin and scaphoid. The buttocks on the other hand, are usually obese and so are the lateral aspects of the thighs and lower legs. The ankles are seldom involved.

*Laboratory investigation.*—Biochemical investigations yield little positive contributory information and in some cases conflicting findings have been reported. Several workers reported some difficulty in the deposition and, to a lesser extent, in the oxidation of fat.[10] The absorption of fat is apparently normal. The levels of blood cholesterol vary from 142 to 330 mgm. %.[10] Those of serum calcium, serum phosphorus,[13] blood sugar,[8, 14] blood urea, nitrogen, uric acid, non-protein nitrogen, creatine and creatinine[10] are all in normal range. The number of cases in whom extensive biochemical investigations have been carried out is not very great, but so far, no specific laboratory findings diagnostic of progressive lipodystrophy have been found. In one of our patients in whom certain endocrine functions were investigated, no abnormalities were found.

*Pathology.*—Although over 100 cases of progressive lipodystrophy have been reported, only a few of the investigators have presented biopsies of skin and subcutaneous tissue from affected regions of the body.[7, 8, 12, 16, 17] Complete autopsies were performed in only two cases, both under 15 years of age,[15, 18] who died from intercurrent infections not associated with lipodystrophy. In spite of the numerous reports of various pathological conditions associated with progressive lipodystrophy, we agree with Harris and Reiser that there are no constant pathological changes except for the lack of subcutaneous fat in the affected areas of the body. The skin and muscle appear normal, both clinically and histologically. On examination, no impairment has been found either in the function of the muscles or in the response to electrical stimulation of either the muscles or nerves. Disturbances of sensory sensation, reflex or vasomotor function have not been reported.[19]

*Etiology.*—Numerous attempts have been made to incriminate various factors as the cause of progressive lipodystrophy but the etiology of this condition remains obscure. There appears to be no hereditary or racial predilection although these have been suggested by some authors.[10, 11] Others[20] have considered that the condition is due to local congenital anomalies, which is unlikely. Brain[25] attributed the cause of lipodystrophy to disturbance of autonomic innervation possibly due to infection. Some

workers considered basal meningitis or hydrocephalus as one of the underlying causes.[22] Others presuppose the presence of some defect in the diencephalic centre, possibly congenital in origin, which manifests itself only when other difficulties arise such as commencement of the menstrual cycle, gestation, menopause, or trauma (due to infection etc.).[14, 22, 23]

*Infections.*—In many cases the onset of progressive lipodystrophy was reported to follow some antecedent infectious disease such as measles, pneumonia, rheumatic fever, mastoiditis etc., but the significance of such infectious diseases in the pathogenesis of this condition is not clear. Many authors consider them merely intercurrent or antecedent diseases.

*Endocrine dysfunction.*—Some fat dystrophies are known to be associated with endocrine dysfunctions: Frohlich's syndrome, Dercum's disease,[39] diabetes, hyperthyroidism, hypothyroidism, Addison's disease, etc. Almost every endocrine system of the body has been considered as the etiological factor underlying progressive lipodystrophy. The pituitary,[10] thyroid,[11, 12, 21] gonads,[8, 9, 22] pineal gland,[24] and hypothalamus have been incriminated in the etiology but there is no concrete evidence to support this nor for the existence of a centre of fat distribution[27] to account for subcutaneous fat changes peculiar to progressive lipodystrophy.

*Neurogenic and trophic changes.*—In several cases the onset of lipodystrophy followed an attack of encephalitis or menginitis. Moreover, some authors considered that there is a definite increase in the incidence of lipodystrophy following acute infections which may affect the central nervous system. Possibly because alterations of fat metabolism have been asociated with various cerebral changes (dystrophia adiposogenitalis), obesity secondary to basilar meningitis, hydrocephalus of the third ventricle, fractures of the base of the skull,[17] a neurogenic etiology has been proposed by some authors.[3, 14, 17, 22, 23] Trophic disturbances have been found in association with progressive lipodystrophy in some patients.[14, 22 to 24, 26] At present the available clinico-pathological findings do not lend support to any of the etiological hypotheses proposed and these must remain simply as theoretical assumptions. The occurrence of somatic, trophic, endocrine and functional aberrations in association with progressive lipodystrophy may be purely coincidental, and not in any way contributory to the causation of this condition.

## TREATMENT

Since the etiology of progressive lipodystrophy is unknown, there cannot be any form of treatment which has a specific clinical basis for its application. The various therapeutic measures tried, comprised administration of thyroid, pituitary and ovarian extracts, massage, electricity, hydrotherapy, bed rest, diet, etc. Overfeeding produces an increase of fat deposits in the lower extremities but no change in the atrophied regions although some authors disputed this.[28, 29] There appears to be no specific general treatment of progressive lipodystrophy. Fortunately the condition is self-limiting[30] and progresses no further when all fat has been lost from the upper part of the body. However, the sequelæ of the disease due to altered appearance usually generate a number of problems which have social, economic and psychiatric implications. The cadaverous appearance of the face which is so characteristic of patients afflicted with progressive lipodystrophy causes them to withdraw from society. Such patients usually avoid crowds, have few friends and do not want to be seen outside their homes in the daylight. It is difficult for them to find employment because both the employer and employees consider that their appearance suggests the presence of some serious disease. Before long, several symptoms such as restlessness, insomnia, phobias, inferiority complexes and other complaints, appear.

Generally, however, in spite of their "sickly" look, these patients enjoy good health and are able to work as well as the normal individual. Surgical reconstruction of the obvious facial defect is sufficient to restore the patient's self-confidence so that he is able to enjoy normal relationships both socially and economically.

*Local therapy.*—Transient improvement has been obtained by the injection of human fat and sheep's suet[6] and of paraffin[16] subcutaneously. These methods are now in disrepute and for the past two decades autogenous grafts have been used to correct the depressed areas on the face. Moskovitz[31] employed strips of fascia lata and fat. Straatsma[32] described the use of transplants of dermis and fat for small defects. Cotton[33] inserted finely cut gluteal fat. Other experimental studies have shown that this latter method leads to greater absorption than when a single large piece of fat is used.[34] In order to

avoid shrinkage of the transplant Eitner[35] used island flaps of skin and fat from the temporal region. For the treatment of hemiatrophy of the face, Byars[36] has described the use of various methods; fascia and dermis with or without fat, or decorticated pedicle flaps inserted through submandibular incisions. Kazanjian[37] found that the best results in hemiatrophy were obtained by the insertion of blocks of dermis, fat and fascia. The graft may be cut into small cubes or applied in one large piece. During the past few years, the insertion of alloplastic grafts such as tantalum sheet and wool, or acrylic implants in depressed areas of the face has enjoyed quite a vogue. Most of these were defects due to trauma. We believe, however, that in due time a final appraisal of these cases will be made and the advantages of autoplastic grafts will result in their use exclusively.

Three patients with progressive lipodystrophy have been treated by us and the most successful result was obtained by the use of large dermal grafts with a small amount of fat. In one case in whom a block of fascia and fat was used, there was marked absorption. However, from the experience of these cases it would appear that dermis grafts alone offer the most permanent æsthetic results because dermis is absorbed more slowly and much less completely than fat. Some of our biopsies taken two years after the insertion of dermis and fat grafts show identifiable elements of the dermis remaining although there was considerable deposition of fibrous tissue in the immediate vicinity of the graft (Fig. 3, D). The possibility of the formation of epidermal cysts in the graft has been completely allayed by the excellent experimental work of Peer and Paddock.[38]

## OPERATIVE PROCEDURE

*General considerations.*—It is hardly necessary to mention that extreme gentleness should be used in obtaining and in trimming the graft, so that tissue damage from trauma and subsequent necrosis may be avoided. In no instance has perforation into the oral cavity occurred while the skin flaps were being dissected from the underlying muscle. However, the possibility of this renders it advisable to separate the skin flaps from the face before removing the dermal grafts so that in the event of perforation reconstruction may be postponed. In our first patient, we used folded sandwiches of fascia lata and fat. In the subsequent two patients, dermis and fat grafts were inserted, and the amount of shrinkage was much reduced. In the future it is planned to insert only sheets of dermis, built up in layers to conform to the size of the defect.

*Determination of size of graft.*—One procedure for obtaining the dimensions of the graft required, is to take an impression of the patient's face and pour a plaster model. The normal contour of the face is then restored with wax and the dermis graft may then be shaped to correspond in size to the wax pattern. An alternative and simpler method is to fashion pads of sponge rubber directly on the patient's face which fill the defects in contour. These may be autoclaved and when the grafts are removed they can be trimmed and built up so that they reduplicate the rubber models almost exactly.

*Donor area.*—In all three cases the measured grafts were taken from the upper lateral aspect of the thigh. A dermatome skin graft 0.008 inches thick was removed after which two pieces of dermis of predetermined size were excised. The epidermal graft was resutured in the defect and a routine pressure dressing was then applied.

*Insertion of the grafts.*—We have used a part of the usual face lift incision for elevation of the skin over the cheeks. This extends from the superior junction of the ear with the scalp into the external auditory meatus behind the tragus, and then emerges to extend down to the junction of the lobule with the skin of the cheek. Thus a most inconspicuous scar is the result. The skin of the cheek is dissected with sharp scissors in a plane just beneath the dermis. This is most important, if free bleeding is to be avoided. Should this be encountered, the cavity is packed with warm saline dressings and firm pressure applied. If this does not control oozing, gauze sponges saturated in a 1:1,000 solution of thrombin may be inserted and external pressure maintained by the assistant while the opposite cheek is being prepared. When bleeding has been controlled, the transplant is inserted in a single large block. Sutures of No. 38 stainless steel wire are placed in mattress fashion at the four corners of the graft and long straight needles are threaded on each end. The needles are passed through the skin of the face at predetermined points, so that the graft will be kept at normal tension and correct position in the cavity. The wire sutures are then tied over small rolls of xeroform gauze.

In all instances, the dermal side of the graft has been applied to the under surface of the skin

of the cheek in anticipation that a firmer degree of fibrosis would unite the two and thus prevent contraction of the implants. As a precaution against infection, a few cubic centimetres of a solution of penicillin containing 25,000 units per c.c., is injected into the cavity before the skin incisions are closed with fine sutures. Because the formation of a hæmatoma is so detrimental to the survival of large implants, a strand of silkworm gut is inserted at the inferior end of the incision to act as a drain for 48 hours.

*Postoperative care.*—Before application of the dressing, the patient's teeth are wired together to aid in immobilization of the operative site. A firm pressure dressing is then applied evenly over the face. A soupy diet rich in calories and vitamins is then given. At the end of two weeks, the wires are removed. The pressure dressing is retained for a week or two longer.

*Complications.*—The most serious complication which may occur is the development of infection. Preventive measures are to be stressed but should it occur, dependent drainage may be obtained by opening the inferior portion of the suture line. Penicillin should be employed generally as well as locally. If a hæmatoma forms in spite of the usual precautions, it should be evacuated by aspiration or re-opening part of the suture line. Failure to do so, if the collection is large, will interfere with prompt revascularization of the grafted tissue which will subsequently atrophy even if infection does not develop. A third reason for failure is the insertion of the graft without mattress sutures to retain the tissue under normal tension during the process of healing. Movement of the facial muscles and jaws will tend to roll the flap into a thick lump. If the cosmetic appearance is unsatisfactory as a result of any of these complications a new graft of appropriate size may be inserted to fill in the defect. This should not be attempted until the reaction from the initial operation has completely subsided. With care the desired result can be achieved by one operation.

The following protocols of the three cases of progressive lipodystrophy which we treated illustrate the application of the principles outlined above.

### CASE 1

Miss E.E., aged 25 years, was admitted to the Plastic Surgery Service complaining of increasing wasting of the face, chest and abdomen (Fig. 1, B). The loss of fat began in her "early teens" and eventually a relative increase in the size of her hips and thighs occurred. At the age of twenty years the patient suffered from an attack of quinsy, complicated by severe septic throat and mastoiditis. Following this illness the thinness of the upper part of the body became more pronounced, but there were no other signs or symptoms. The functional inquiry was entirely non-contributory with the exception of the presence of some dysmenorrhœa in the few months preceding admission to the hospital.

Physical examination revealed extreme loss of fat in the face (Fig. 1, B), chest, and upper abdomen. The hips were well developed with normal distribution of fat. No muscular atrophy was present. Examination of all systems produced no evidence of abnormality. Laboratory investigations revealed no abnormal findings.

*Operation.*—Under spinal anæsthesia fat-and-fascial grafts were removed from the right and left thighs and inserted, under local anæsthetic (novocaine 2%), into subcutaneous pockets formed by raising the skin of the right and left cheeks through modified face lift incisions. All sutures were removed on the 10th postoperative day. A hæmatoma had formed in the right cheek and aspiration was necessary on several occasions, however, no infection developed. The patient was discharged three weeks following operation. She was re-examined at intervals for six years and the marked overfilling of her cheeks which was carried out intentionally to allow for subsequent shrinkage, gradually diminished until the appearance shown in Fig. 1, D was obtained. Her social readjustment and mental outlook have improved steadily and at present she is well adjusted in spite of a small irregularity of the left cheek which she does not consider of sufficient importance to have corrected.

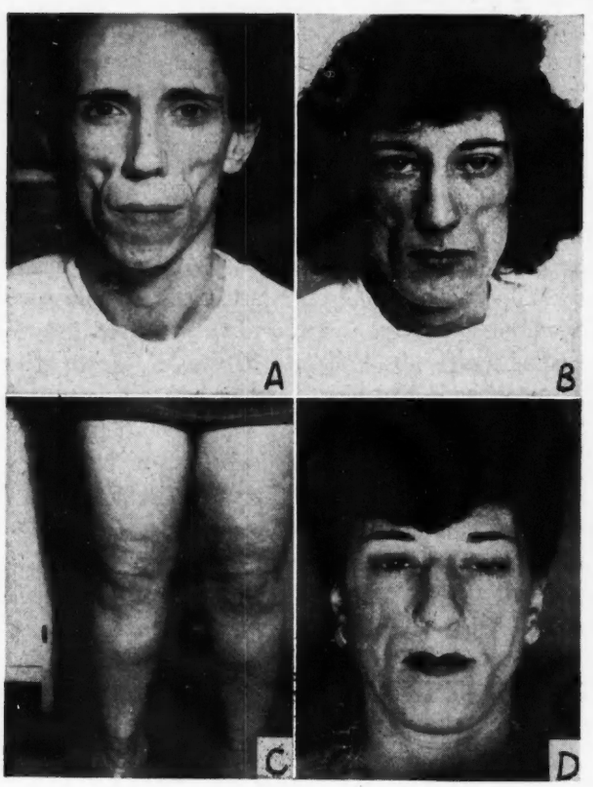


**Fig. 1.** — A.—Case 2, preoperative showing the cadaverous appearance suggestive of the presence of some grave illness. B.—Case 1, preoperative. Note the sunken cheeks and relative prominence of the orbicularis oris muscle. C.—The very obese lower extremities of Case 2. Such disproportion is not infrequently found in this disease. D.—Case 1 taken six years after the corrective operation.

CASE 2

Mrs. G.S., 37 years old, was admitted to the Plastic Surgery Service with the complaint of extreme thinness of the face and thorax for the past 20 years (Fig. 1, A) and dizziness for about three years prior to admission. The onset of the "thinness" appeared to have followed an attack of rheumatic fever at the age of 16 years. Every attempt to gain weight by increasing her food intake resulted in an increase in the deposition of fat in the lower part of the body, particularly the hips and legs. The face, neck, chest, shoulder and arms remained very thin. For the past three years she had been complaining of headaches and dizziness. The latter symptoms were most frequently noticed when she was in crowded places. She claimed that these symptoms were considerably improved by a course of liver and iron therapy.

Physical examination revealed gross absence of subcutaneous fat on the head, arms, thorax and upper abdomen. Her muscular development was excellent. On the other hand her hips and legs were abnormally obese, (Fig. 1, C). The blood pressure was within normal limits and all laboratory investigations were essentially negative. An endocrinological study was performed by Dr. J. S. L. Browne. The pregnandial excretion was found to be normal, indicating normal ovarian function.

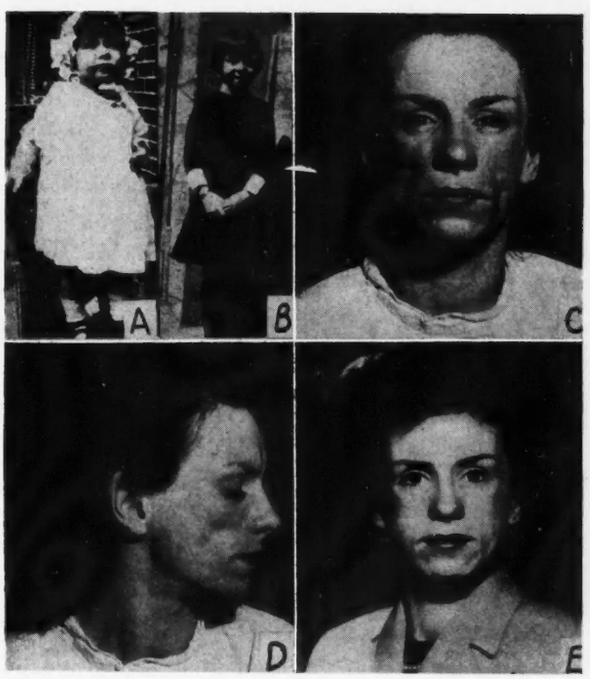


**Fig. 2.**—A. and B.—Case 3, showing the normal appearance at the ages of two and six years respectively. C. and D.—Her appearance at 27, just preoperatively. E.—Four months postoperatively.

*Operation.*—Under spinal anæsthesia, dermis and fat grafts were removed from the left thigh and inserted in the usual manner under the elevated skin flaps of the cheeks. Here again a small hæmatoma formed in the right cheek and was expressed a few days postoperatively, after removing a few sutures at the lower part of the incision. No infection occurred. Considerable shrinkage took place during the course of a year and she will require supplementary grafts to overcome the depression in the region of the naso-labial folds where the grafts were displaced backwards.

CASE 3

Miss M.C., 27 years old, was admitted to the Plastic Surgery Service with the complaint of wasting of skin over the face , arms and upper trunk, which started at the age of eleven and gradually progressed to her present appearance (Fig. 2, C and D). She was perfectly well until eleven years of age and had only measles and whooping cough at the age of 6 years (Fig. 2, B). Since then she has been in perfectly good health and started work at the age of 20 years. Because of her appearance she formed few friends, avoided crowds, and would not go out during the day except when going to work. She presented herself and inquired if something could be done for her appearance so that her social and business life would be rendered more agreeable.

Physical examination revealed a complete absence of external fat on the head, arms, thorax and upper abdomen. The breasts were well developed but only glandular tissue could be palpated. Her musculature development, due to lack of fat, appeared to be even more prominent than normal. Her hips and legs were of normal feminine configuration. The usual laboratory investigations were entirely within normal limits. Biopsies of the skin of the face and arm revealed a complete absence of subcutaneous fat on histological examination (Fig. 3, A and B). On the other hand, the histological examination of the skin and subcutaneous tissue of the thigh was completely normal grossly and histologically.

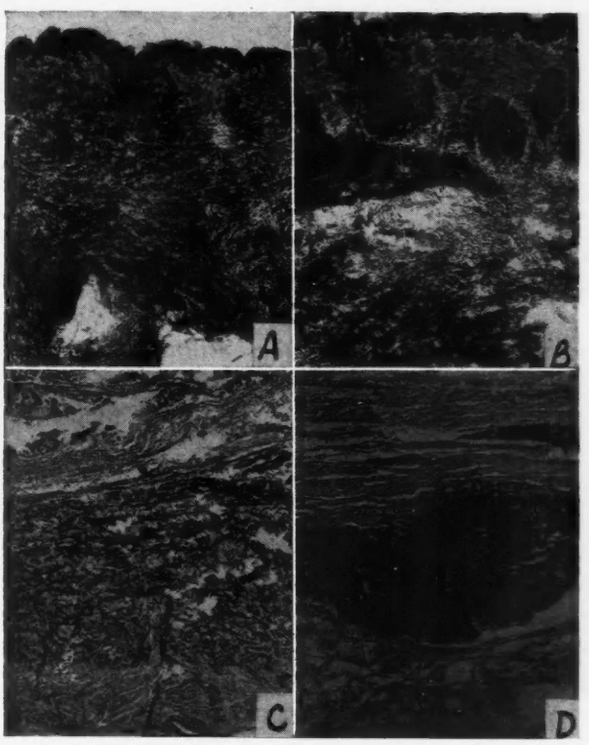


**Fig. 3.**—A.—Biopsy of the skin and subcutaneous tissue of the cheek showing the absence of subcutaneous fat (Case 3). Scharlach R fat stain. Magnification x 40. B.—Biopsy of the skin and subcutaneous tissue of the arm showing the complete absence of subcutaneous fat which would be represented by solid black in the section (Case 3). Scharlach R fat stain. Magnification x 40. C.—Biopsy of the dermal graft taken from Case 3 four months after implantation under the skin flap of the cheeks (Case 3). Verhoeff's elastic tissue stain. Magnification x 40. D.—Biopsy of the dermal graft taken two years after implantation. The dark-staining mass in the centre is made up of the persisting elastic tissue fibres. Verhoeff's elastic tissue stain. Magnification x 100.

*Operation.*—Under general anæsthesia, dermis grafts containing a minimal amount of fat were removed from the right thigh and inserted in the customary manner under the elevated skin flaps of the cheeks. Continuous

pressure was applied to the right cheek while the operation on the left cheek was carried out. The healing was prompt and uneventful. A biopsy was obtained from the dermis and fat graft in the cheek four months following operation and histological examination revealed no trace of epithelial elements, some scar replacement of the dermis, and absence of fat (Fig. 3, C).


## SUMMARY

1. Progressive lipodystrophy is a disease which is more common in females. It usually starts in the first or second decade of life and is limited to the upper half of the body.

2. Laboratory investigations have revealed no diagnostic findings which are specific for this condition. Absence of the subcutaneous fat in the affected regions of the body is the only constant histopathological finding.

3. Certain infectious diseases, endocrine dysfunctions and neurogenic disturbances have been proposed by various investigators as possible etiological factors in this disease but no conclusive proof of any of these claims has been produced.

4. Although this disease is self-limiting it leaves the person with a "consumptive look" which makes it difficult for him to obtain work and drastically curtails his social activities. The development of inferiority complexes and of other psychological disturbances is almost inevitable.

5. Various types of general therapy have been unsuccessful so far. Local surgical therapy designed to fill in the sunken cheeks is a definite step toward reconstruction of the most obvious defect. Dermis or dermis and fat grafts are the most satisfactory autoplastic substances which may be used. Hæmostasis must be thorough; the graft should be sutured under tension and the jaw completely immobilized to permit fixation of the graft in correct position and to promote more rapid healing.

6. Sheets of dermis built up in layers and fashioned to conform to the shape of the defect appear to give the most satisfactory results. The techniques of operation and the possible complications are discussed.

7. Detailed studies of three cases of this uncommon condition have been presented and the method of treatment described.



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# THE TREATMENT OF CARCINOMA OF THE CERVIX UTERI*


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THE purpose of this paper is to discuss certain points of the natural history of the disease, to review some of the published literature on the treatment of the disease and to present the results obtained at the British Columbia Cancer Institute by radiation therapy.

Carcinoma of the cervix is the second most common form of cancer in women. The disease occurs commonly in women between the ages of 40 and 50. It can occur before puberty, but before the age of 30 and after 60, the disease is rare. The disease occurs at an earlier age than carcinoma of the body of the uterus. There is no association between the number of pregnancies and the development of carcinoma of the cervix. The most common symptoms are vaginal hæmorrhage and discharge unrelated to the menstrual periods.

* Read at the Seventy-ninth Annual Meeting of the Canadian Medical Association, Section of Radiology, Toronto, June 24, 1948.

Three main clinical types are described—the cauliflower, the ulcerative and the infiltrating or nodular. The anatomical extent of the disease is classified into four stages according to the plan adopted by the League of Nations.

TABLE I.

CARCINOMA OF THE CERVIX

| *Stage* | *Extent of disease* |
|---|---|
| I. ..... | Cervix only. |
| II. ..... | (*a*) Parametrium, |
| | (*b*) Vagina—upper two-thirds, |
| | (*c*) Endocervix and body of the uterus. |
| III. ..... | (*a*) Parametrium to pelvic wall. |
| | (*b*) Vagina—lower third, |
| | (*c*) Isolated pelvic metastases. |
| IV. ..... | (*a*) bladder, |
| | (*b*) rectum, |
| | (*c*) Distant spread. |

The vast majority of carcinomas of the cervix are of the squamous-cell type, those arising from the endocervix are often adenocarcinomas. The disease remains localized to the cervix and within the pelvis for a considerable time.

Carcinoma of the cervix spreads in the following ways. (1) By direct extension; endocervical growths spread up into the uterus. Ulcerative growths of the cervix spread into the vagina and parametria. (2) By involvement of the lymphatics. In this connection it is important to bear in mind the anatomy of the lymph glands of the pelvis (see Fig. 1). (3) By metastases. When this occurs the disease has usually reached a terminal stage. Metastatic deposits can be found in any organ of the body, commonly the liver, lungs, brain and vertebral column. The fact that distant spread occurs late in the course of the disease should make it possible, with improved methods of treatment, to cure a larger number of patients during the period when the disease is limited to the pelvis.

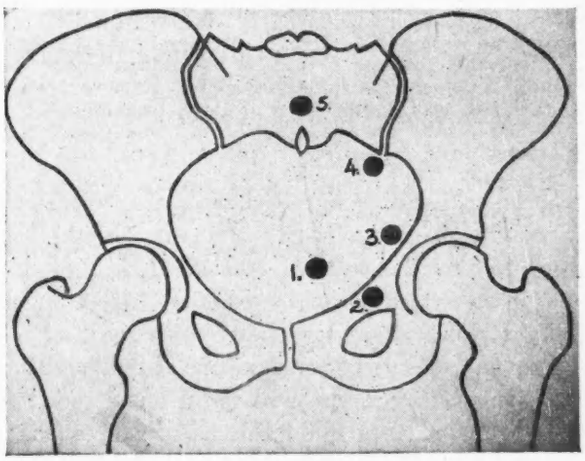


**Fig. 1.**—Showing distribution of lymph glands. (1) Nodes in the parametrium. (2) Obturator lymph node near the obturator canal, usually grouped with the external iliac nodes. (3) Lymph nodes along the external iliac vessels. (4) Internal iliac nodes about the internal iliac vessels near the sacro-iliac joint (hypogastric nodes). (5) Nodes near the promontory of the sacrum.

The diagnosis, as a rule, is easy. The symptoms are sufficiently characteristic to give a lead as to the site of the tumour. To establish the diagnosis and the extent of the disease the following examinations should be done—palpation of the abdomen, bi-manual vaginal examination with the right and left hands, rectal examination, inspection and biopsy. Cystoscopic examination and retrograde pyelography are indicated in all cases to determine whether the bladder and ureters are involved.

A review of the published literature on the treatment of cancer of the cervix reveals a wide variety of opinions on the best methods to use and it is not intended to enter into any controversy, but to point out as Buschke and Cantril[1] have done that the particular type of technique used is less important than the thorough application of certain general principles of treatment and their modification to suit the needs of each individual case. However, it is obvious that individual preference for a certain type of treatment will always be with us because concentrated effort by individuals has resulted in the technique that is used today in many different places.

The first method of treatment to be practised was surgery, and the technique of the operation, except for minor modifications, has been established for many years. It appears that the good results obtained by competent surgeons are no better than those of competent radiotherapists in Stage I cases. A very important aspect in the surgical management of the disease is that only 10% of all cases of carcinoma of the cervix are in Stage I and only a small number of these are suitable for operation, so it would seem that surgery has a very limited place.

Meigs has operated on more than 100 cases without any deaths. In his earlier cases the morbidity was high due to ureteral fistulas; this complication has been overcome by a refinement of technique. Meigs does not advocate that surgery should be adopted generally but rather that the treatment of choice should be radiotherapy. Surgery is possible in Stage I and

some Stage II cases but is impractical for Stages III and IV.

Radium in the treatment of cancer of the cervix has been used since 1905, but it was not until 1909 when Dominici discovered the principle of filtration that it came into general use. Radium treatment practised today follows or is a modification of two well-known techniques. They are the Stockholm and the Paris techniques.

The Stockholm technique, developed by Heyman at the Radiumhemmet, is essentially one in which relatively large quantities of radium are left in place for two or three periods of 24 hours each and the Paris technique, developed by Regaud and Lacassagne, is where continuous irradiation is provided by smaller quantities of radium left in place several days. In the Stockholm technique an intra-uterine tube and two or more vaginal applicators are used on three occasions to give a dose of about 2,600 mgm. hours to the uterus and 4,500 mgm. hours to the vagina. The second application is a week after the first and the third two weeks after the second. In the Paris technique 66.66 mgm. are used, equally divided between the uterus and vagina for a period of about 120 hours to give a total dose of about 8,000 mgm. hours.

Radium treatment administered by either method results in an 80 to 85% five-year survival in Stage I cases. It is impossible with radium, however, to deliver a sufficient dose to any part of the tumour that may be near the pelvic wall, so it is necessary to treat these areas by means of x-ray therapy. Regato[2] in his book states that if internal irradiation can be called the most important single factor in the treatment of advanced cases, a thorough external roentgen-therapy is the most important single factor in the treatment of advanced cases. Paterson,[3] on the other hand, says that the best palliation of advanced cancer of the cervix is obtained by giving a full course of radium.

If x-ray therapy is to be given before or after a full course of radium treatment, the x-ray fields must be directed so that the zone in the mid-line to be or already treated by radium receives no radiation. It is necessary, therefore, to leave a space in the mid-line at the front and back. The width of this pace will vary from 3 to 5 cm. according to the amount of radiation delivered by the radium.

The design of radium applicators for use in the vagina has been investigated by many workers. Tod and Meredith[4] working at Manchester, designed special rubber ovoids to give a certain dose at different points in the pelvis. They point out that the dosage is limited by the tolerance of normal tissues. For the purpose of their study they took the point of limiting tolerance as being in the paracervical region 2 cm. lateral to the uterine canal and 2 cm. above the mucous membrane of the lateral fornix. This is called Point "A", and is where the uterine artery crosses the ureter. Point "B" is designated as being 5 cm. from the mid-line at the same level as "A". Point "B" would represent roughly the obturator node. The rubber ovoids used are large, medium and small, according to the size of the vagina. The large ovoids contain 5 units of radium, the medium 4 and small 3—likewise the long uterine tube contains 2-2-1 units, the medium tube 2-1 units and the short tube 2 units. The uterine tube is thin so as to avoid over-dilatation of the cervical canal. The ovoids are placed as far out in the vault as possible and are held apart by a rubber spacer. The dose delivered to Point "A" is 7,200 "r" and at Point "B" 2,500—3,000 "r" in one week. A course of x-ray therapy lasting 5 to 6 weeks directed to the lateral pelvic wall on each side leaving untreated a space 5 cm. wide in the mid-line is then given—the dose at Point "B" from x-ray therapy being about 4,000 "r", so that the total dose would be about 6,500 "r".

Tod[5] states that the addition of x-ray therapy to Stage I and II cases already treated by radium does not improve the survival rate. Sandler[6] has pointed out that the main factor affecting dosage by radium is the size of the vagina and the disposition of the radium in the vaginal applicators, and that too large a dose to the paracervical region will give poor results because of what has been called the "supra-lethal effect", in other words, the vaginal mucous membrane is not the point of limiting tolerance.

Neary[7] states that the vaginal radium should be placed in the mid-line. He uses two lots of radium, 140 mgm. each separated by 9 mm. of platinum in a very ingenious device provided with adequate filtration to protect the rectum and bladder. The radium used in the uterus is in the form of a 50 mgm. tube. Neary designed this applicator because he contends that no radical change in the dose delivered is to be expected by variation of the Stockholm or Paris techniques. No published results are yet available of this method of treatment.

Most authorities agree that in the presence of pelvic infection x-ray therapy should be given before the radium treatment, in fact in some clinics regardless of whether infection is demonstrable or not x-ray precedes radium.

The narrowing of the vagina which results following x-ray treatment is interpreted by some workers as a good thing, by others that it seriously interferes with a proper application of the radium treatment, it seems necessary, therefore, to apply the radium before too much contraction has occurred in the vagina. In a number of clinics in the United States transvaginal roentgen therapy is used in place of radium and the proponents of this method state that it is superior to radium, but it cannot be used in all cases, for example, where there is vaginal atresia or pus in the uterus. Regato[8] states that transvaginal roentgen

therapy with 140 KV is the treatment of choice in carcinoma of the cervical stump. Erskine[9] feels that this method gives a better distribution of radiation than with radium and that the clinical results are better.

The complications which arise from over-treatment with radium are usually in the rectum, seldom in the bladder. The complication may be one that was anticipated and unavoidable or it may be due to inaccuracy in technique. Late rectal reactions occur 6 to 12 months after treatment. The symptoms are pain and bloody discharge. On palpation an indurated ulcer can be felt on the anterior rectal wall at the level of the cervix. The condition may clear up by itself or go on to stricture necessitating a colostomy. A certain amount of rectal reaction is present in all adequately treated cases, if it is absent, it is probably an indication that the radium treatment has been insufficient. Fibrosis of the base of the bladder does occur. Stricture of the ureters is usually interpreted as being due to growth.

Regarding the histology of the tumour, both squamous cell and adenocarcinomas are radiosensitive and radiocurable. Graham[10] in a study of vaginal smears taken during and after radiation treatment found she could predict in 88% of the cases whether the response to the treatment had been good or bad. Glucksmann and Spear[11] point out that in comparing the results of treatment in various centres it is important to know the grading of each tumour, because the results of treatment of undifferentiated or anaplastic tumours are poor, although the immediate response may be satisfactory.

Koller[12] contends that the type of response to radiation cannot be predicted from a biopsy taken before treatment and he says that it is unsafe to use serial biopsies as a basis for deciding on the type of treatment—surgical or radiological. He also feels that all early cases should be treated as if the disease had spread beyond the cervix. Cytological observation of metastatic lymph nodes shows that from a biological standpoint adequate treatment of lymph node metastases is possible, although the radiation response in lymph nodes differs from that seen in the primary tumour. This is a very encouraging observation by Koller as many radiologists have felt that it is impossible to sterilize carcinomatous lymph nodes with the x-ray therapy used at the present time.

Regaud published, many years ago, his results in the treatment of carcinoma of the cervix. No great change is evident in the results published elsewhere.

TABLE II.
PARIS REGAUD 1922–1926

| *Stage* | *Number of cases* | *5–year survival* | *Percentage* |
|---|---|---|---|
| I. | 29 | 23 | 79 |
| II. | 121 | 50 | 41 |
| III. | 179 | 50 | 27 |
| IV. | 51 | 1 | 2 |
| Total | 380 | 124 | 32 |

The reason that only 80% of State I cases are cured is because undetected lymph nodes are invaded in 15 to 20% of the cases.

At the British Columbia Cancer Institute a total of 338 cases of carcinoma of the cervix have been seen from 1938 to 1947. Some of them have been referred for follow-up examinations after receiving their treatment elsewhere. The cases available for a study of five-year survival are from 1938 to 1942, a total of 126 cases.

TABLE III.
BRITISH COLUMBIA CANCER INSTITUTE 1938–1942

| *Stage* | *Number of cases* | *5-year survival or over* | *Percentage* |
|---|---|---|---|
| I. | 25 | 21 | 84 |
| II. | 38 | 13 | 34 |
| III. | 32 | 4 | 12 |
| IV. | 31 | 2 | 6 |
| Total | 126 | 40 | 31 |

An analysis of the grading of the tumours shows that 85% of the tumours were Grade 3 and 4 and that 55% were Grade 4. Only one case was Grade 1. These facts corroborate the evidence that the survival period for patients with undifferentiated tumours is short although the immediate response may appear to be satisfactory.

The treatment given at the British Columbia Cancer Institute has been radium by a modified Stockholm method and x-ray therapy. The radium is put in bakelite colpostats of varying sizes, filtered with lead, two or more applicators being used, depending on the size of the vagina. An intra-uterine tube to fill the cervical and uterine canal is always used when the

external os can be found. The total vaginal and uterine dose has varied from 5,500 to 8,600 mgm. hours over a period of three weeks. X-ray films are taken on all patients showing the radium in position, so that a proper alignment of the x-ray fields can be made.

X-ray treatment has generally followed the radium treatment after an interval of 2 to 3 weeks. The x-ray treatment with 400 KV takes about four weeks and a dose of 2,800 to 3,500 "r" is delivered to the parametria. The x-ray treatment fields vary according to the size of the pelvis, a free space in the mid-line is not treated, four fields are usually employed, two anterior and two posterior; occasionally lateral fields are used.

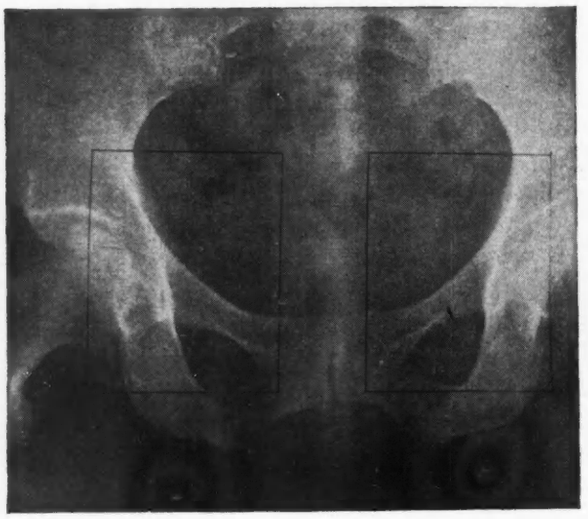

**Fig. 2.**—X-ray film of the pelvis showing treatment fields marked out.

It is apparent from the cases seen at the British Columbia Cancer Institute that the number of patients with advanced carcinoma of the cervix remains high. The conclusion that one arrives at, therefore, is that patients must be urged to seek advice earlier than they do at present.

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## PREGNANCY AND TUBERCULOSIS*

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IN considering the problem of pregnancy complicated by pulmonary tuberculosis, we must also remember the factors of labour, puerperium, and the period following puerperium.

Roughly speaking, 50 to 100 years ago[1] pregnancy was believed to exert a favourable influence on tuberculosis. Twenty-five to 50 years ago the reverse was the accepted belief, and early termination of pregnancy was the method of choice. During the past 25 years the prevailing medical opinion is that with adequate treatment and good teamwork between the phthisiologist and the obstetrician, a more conservative attitude may be adopted.

Congenital tuberculosis is rare, although some 47 authentic cases had been collected. Sitzenfrey, as quoted by Williams, "has demonstrated the presence of bacilli in the interior of the ovum while still within the Graafian follicle".

The ideal set-up would be a hospital devoted exclusively to the care of tuberculous women during the pregnancy, labour, puerperium, and a year or so following the puerperium. With the modern methods of surgical treatment for most cases of pulmonary tuberculosis, these patients can be brought through their pregnancy, labour, and the puerperium, with the statistics for mortality and morbidity being practically no worse than that shown by the female patient of similar age and similar lesion without pregnancy.

In the Seaview series covering 231 cases of pregnancy and tuberculosis, the mortality was 36%; the mortality for 5,470 woman patients as

*Presented at Clinical luncheon, Grace Hospital, April 20, 1948.

controls was 33%. Re-activation of tuberculosis may be expected in a small percentage of cases. It is probably more from strain of lactation and the care of the infant than from the pregnancy and puerperium.

In cases of bilateral pulmonary tuberculosis with positive sputum, where surgical treatment is not suitable, prognosis is not so good. Cases of laryngeal tuberculosis do badly.

### TYPE PROBLEMS

1. A case of arrested pulmonary tuberculosis or one that has had successful collapse therapy and marries. Should she be allowed to become pregnant?

She may safely go through pregnancy two years after the tuberculosis has become arrested. If she becomes pregnant during the maintenance of a successful pneumothorax, the treatment should be continued until at least a year after delivery.

2. A woman in the first trimester of pregnancy is found to have pulmonary tuberculosis. Should pregnancy be interrupted?

If the tuberculosis is still in the treatable stage, the pregnancy should not be interrupted. If tuberculosis is very extensive and beyond treatment by collapse therapy, the pregnancy should be interrupted.

3. A woman in the second or third trimester of pregnancy is found to have pulmonary tuberculosis. Here interruption of pregnancy is contra-indicated, especially if the case is suitable for collapse therapy. The patient should be kept in a hospital or sanatorium for three to six months after delivery. The pregnancy should not be allowed to go past term; lactation is not permitted for any of these cases, both from the point of view of the strain on the mother and possible infection of the child, not through the milk, but by contamination.

How to conduct labour where a patient is at, or nearly at full term? As soon as the cervix is dilated to the extent of a 50-cent piece, *i.e.*, 2 to 3 cm., scopolamine and demerol should be used. Give the patient all the time she needs for the first stage. However, as soon as the dilatation is complete, or nearly complete, rupture the membranes, if they are not already ruptured. The second stage must be made as short as possible.

In a cephalic presentation, application of forceps and episiotomy should be resorted to. Here one can use local and gas oxygen anæsthesia. If the breech is presenting, more or less the same routine is to be followed, *i.e.*, do not hurry with the first stage of labour, but make the second stage as short as possible. If necessary, use forceps for the aftercoming head. The aim should be to carry out all procedures with the minimal amount of shock and hæmorrhage.

One must keep in mind the possibility of excessive post-partum bleeding. According to one author the incidence is 13% as compared with 2% of the non-tuberculous patient. If the case is one suitable for pneumothorax, she must receive the necessary fills during the puerperium. However, in all cases a tight binder is essential.

Now, if pregnancy has to be interrupted during the first trimester, that can usually be carried out in one sitting. In the second trimester, hysterotomy is the method of choice.

As regards the question of sterilization, if a nullipara, be very conservative, as the picture may be much better after the patient has had a good course of sanatorium treatment. In a patient who has already had her family and has advanced tuberculous lesions, contraceptives are hardly the method of choice. Sterilization is the proper approach.

The prognosis for the baby is usually good. Matthews and Bryant reported a follow-up of 579 children; 556 were alive 15 years after birth; of these 501 were in good health (86.5%), 55 were below par, and only in 9 cases was tuberculosis present or suspected. Blisnjanskaja, as quoted by Jameson, from a study of 23,000 children born to tuberculous mothers and sent to the country, found that only 7 developed tuberculosis.

### CASE REPORT

Mrs. M., aged 30 para 4, Rh negative: husband, Rh positive.

First pregnancy was more or less without complications. Second pregnancy was a spontaneous abortion. September 28, 1946, the third baby was born six weeks premature; it died October 3. The patient consulted me for a fourth pregnancy in December, 1947, when she was about 10 weeks pregnant. A report from Dr. Bruce Chown, at this time was as follows: "Mr. M. is a Group A, Rh positive, almost certainly homozygous, and Mrs. M. Group A, Rh negative. We received a blood sample from Mrs. M. first on April 17, 1946. We could not demonstrate any antibodies in this. She gave birth to a premature baby. At the time of death it was mildly jaundiced. We were unable to demonstrate antibodies in the baby's blood taken at autopsy, but the microscopic sections showed evidence of excess blood destruction with deposition of iron in liver and spleen. Mrs. M.'s blood on October 8 had an anti-Rh antibody with a titre of 1:16. I do not think we can say for

certain that the baby died of erythroblastosis. The present fetus has a poor prognosis.''

Hysterotomy and sterilization was done on January 5, 1948, in Grace Hospital and Dr. Chown's report was as follows: ''The fetus was a female weighing 83 grams with the crown-rump length of 107 mm. and a crown-heel length of 154 mm. The placenta and membranes weighed 86 grams. We were able to obtain 2 c.c. of blood from the fetal end of the cord. The fetus was Group O, N, Rh positive, $R_1r$, CDe.cde. The cells did not show evidence of maternal antibody having crossed the placenta, nor were we able to demonstrate any antibody in the serum of the fetus. On the other hand the maternal antibody had a titre of only 1:2 so that it might have been too weak for demonstration in the fetal circulation. Autopsy was performed on the fetus and histological studies made of all tissues but no abnormalities were found.''

Mrs. M. made a good recovery, and was discharged January 16, 1948. She was not suitable for pneumothorax or thorocoplasty, and was re-admitted to Central Tuberculosis Clinic. Sputum continued positive although she had gained some weight.

In this case, decision as to what was best to do was comparatively easy to make on account of the poor prognosis given by Dr. Chown. Both he and Dr. Scott of the Central Tuberculosis Clinic, who had treated the patient for bilateral tuberculosis, agreed that the pregnancy should be terminated.

About 2½ months after termination of the pregnancy, Dr. Scott reported as follows: ''Disease shadows can be seen to be bilateral. She has about an ounce of purulent sputum daily, and it is positive for tubercle bacilli. Patient is running a slight fever and looks poorly. Because of this slow progression of disease over a period of years, we still feel that there was justification here for this therapeutic interruption of her last pregnancy.''

Because of the Rh factor problem and the bilateral advanced pulmonary tuberculosis, sterilization, as well as termination of pregnancy, was decided upon.

216 Kennedy Street.

## CYCLOPROPANE IN CÆSAREAN SECTION*

**J. A. Brown, M.D.**

*Regina, Sask.*

THIS paper is to report our local experience over the past eight years, with an anæsthetic technique which employs cyclopropane without preliminary sedation and requires the utmost in co-ordination or teamwork between the surgical and anæsthetic staff. The literature on cyclopropane in Cæsarean section is very limited. One must conclude that this agent is not generally accepted as an ideal one by obstetricians or anæsthetists, or that the method of using this agent has not been satisfactory, or probably satisfactory methods have as yet escaped publicity.

* This paper was presented to the joint meeting of The American Society of Anæsthesiologists Incorporated and the Western Divisions, Canadian Anæsthetists' Society, at the Regina and District Medical Society dinner at Regina, April 23, 1948.

Cæsarean section, to be successful, requires an operating team of surgeon, anæsthetist, assistants, scrub nurses, floor nurses and a physician to take care of the baby, all working together as one unit. The ideal anæsthetic for Cæsarean section should provide anæsthesia safely and satisfactorily to the mother, while subjecting the fetus to little or none of the agent's toxic effects. The anæsthetic should at all times be under the control of the anæsthetist; it should provide good abdominal muscle relaxation and contraction of the bowel; it should provide maximum oxygen supply; the baby should cry spontaneously immediately after delivery; the uterus should contract well and bleeding should be minimal.

Our experience in Regina with cyclopropane as the anæsthetic in Cæsarean section now totals 378 cases. Two different methods of administration of this agent were used. Prior to 1940, 102 cases were handled as follows: the patient was managed much as in any other operative case; preliminary sedation was usually employed; the patient, after being brought to the operating room, was first anæsthetized, then prepared for the commencement of the surgical procedure. Since 1940, 276 patients have been handled more satisfactorily in a slightly different way. Briefly, this involved anæsthetizing the patient rapidly with cyclopropane, after all preparations had been completed. This change in procedure has resulted in an appreciable reduction in time from the start of the anæsthetic until the baby was delivered, with consequent fewer occasions for resuscitation of the infant.

Briefly, our aim is to administer the smallest amount of a volatile and rapidly acting anæsthetic agent to the mother, prior to the moment of birth. We assume that any anæsthetic agent reaching the fetus is apt to be toxic to it. We can only hope to employ the least dangerous and use minimal amounts.

### Anæsthetic Technique

*Preparation.* — One-half hour prior to the commencement of the operation, the mother is given hyoscine (scopolamine) gr. 1/200 hypodermically. This drug is administered for its drying effect on the respiratory mucous membranes and it probably supplies also a slight amnesic effect without physical depression. Nostrils and pharynx are then sprayed twice, using a bland oily mixture in a fine mist. This

is to overcome the usual sensation of dryness and tickling of the throat following hyoscine without morphine, and to minimize the possibility of coughing which would delay and complicate smooth and rapid induction of anæsthesia. With the patient on the operating table the anæsthetist takes advantage of the time required for surgical preparation and draping to chat with the patient and reassure her, explaining what is going on and why, as well as invoking her confidence and co-operation for the anæsthetic induction to follow shortly.

*Induction.*—Following full surgical preparation and draping, with all trays, tables, instruments and personnel ready and in absolute silence, cyclopropane is administered in the concentration of approximately 40% in oxygen. The patient is asked to relax fully, breathe naturally and to expect to be asleep after only a few breaths. The time is noted. The concentration of cyclopropane is kept at approximately 40% until the onset of the second plane of third stage of anæsthesia. At this instant, the "go" signal is given to the surgeon; the time is again recorded. Anæsthesia is maintained in light second plane until the baby is delivered and the cord clamped.

*Maintenance.*—From the moment the baby is delivered and the cord clamped, the anæsthetist is free to deepen the anæsthetic level as necessary, and the mother is usually his only concern. If, however, the baby shows unsuccessful respiratory efforts, the anæsthetist is prepared at once to turn over the mother's anæsthesia to someone else, at least temporarily, and devote himself to the resuscitation of the newborn. He is equipped to pass immediately a No. 1 vinyl portex endotracheal catheter through which he can pass a 10 F. rubber catheter to suction out the main bronchial tree, and also through which he can administer regular oxygen ventilation of the lungs by gentle manual bag pressure, or by an automatic positive and negative pressure resuscitation apparatus. Such procedure is very rarely found necessary but is always in readiness. A baby who does not breathe spontaneously almost invariably has bronchial or tracheal obstruction due to mucus.

The mother is given a sedative by hypodermic, such as pantopon gr. 1/3, to ease her postoperative recovery as soon as the baby is delivered. A supportive intravenous of 5 or 10% dextrose-saline fluid drip is routinely commenced at this stage. Blood transfusion is available if indicated.

### SURGICAL PREPARATION

In elective cases the patient is admitted to hospital one to three days prior to the date of operation, during which time her physical status is completely reviewed and necessary laboratory procedures completed. The evening prior to operation, abdominal and perineal preparation is completed and she is given a mild barbiturate. On the morning of the operation she is given a saline enema, the skin is prepared with ether and alcohol and is covered by a sterile towel, catheterization is done and the catheter is left *in situ*. One-half hour prior to the scheduled operative time her hypodermic of hyoscine gr. 1/200 is given.

On the operating table the bladder is again drained and the catheter removed. A pillow is placed under the thighs for comfort and abdominal relaxation, and the abdominal wall is prepared with an aqueous antiseptic such as zephiran chloride. This procedure, in the case of a conscious patient, is important as all tinctures are irritating, especially if they escape to the vulvar area, and such irritation will interfere with the smooth induction of anæsthesia. When everything is ready induction is begun. The average induction time is between three and one-half to four minutes, following which, and when second plane of third stage of anæsthesia is reached, the anæsthetist signals the surgeon that the operative procedure may be started.

No attempt will be made to give a full description of the operative procedures used. I shall indicate merely two special points, as follows: (1) In the interests of rapid delivery of the fetus, bleeding points in the abdominal and the uterine wall are temporarily ignored, or are simply clamped with hæmostats. (2) Following delivery of the fetal head from the uterine cavity, ten units of pitocin are injected into the uterine muscle and 1 c.c. (1/320 gr.) of ergotrate is injected intramuscularly by an attendant. This routine procedure insures prompt contraction and tonus of the uterine body and produces spontaneous delivery of the placenta, with negligible blood loss and without removal of the uterus from the abdominal cavity.

### Summary of Cases

The following sections were performed by 20 different surgeons, some of whom performed only the occasional operation, others having wide surgical experience. The anæsthetics, however, were administered by five fully qualified anæsthetists using essentially the one technique.

The Indications for Operation Were as Follows

| | |
|---|---|
| Contracted pelvis with cephalic presentation | 290 |
| Contracted pelvis with breech presentation | 11 |
| Contracted pelvis with toxæmia | 4 |
| Obstructing fibroids or other pelvic tumour | 6 |
| Repeat classical Cæsarean | 25 |
| Central placenta prævia | 7 |
| Partial placenta prævia with coincident indications | 11 |
| Previous pelvic floor repair | 5 |
| Primary inertia | 1 |
| Twins, fibroids and toxæmia | 1 |
| Mitral stenosis, toxæmia, contracted pelvis | 2 |
| Transverse presentation | 3 |
| Abruptio placenta | 2 |
| Face presentation | 2 |
| Malformation of pelvis | 3 |
| Ruptured uterus | 2 |
| Advanced rheumatic heart disease and decompensation | 2 |
| Large stillborn fetus | 1 |
| Total | 378 |

The Types of Cæsarean Were

| | |
|---|---|
| Classical | 306 |
| Low | 63 |
| Cæsarean hysterectomy | 6 |
| Classical Cæsarean and myomectomy | 3 |
| | 378 |

In this series there was one maternal death. This patient, aged 37 years, had had a classical Cæsarean section some years previously and was admitted to hospital with a rupture of the uterus which had occurred 48 hours previously and with a dead fetus. She received 2,000 c.c. of blood and at operation a rupture of the anterior wall of the uterus was found with a dead fetus lying in the abdominal cavity. The fetus and placenta were removed and uterine wall closed. She died two and a half days later. Her temperature at the time of death was 106°. Post-mortem revealed pulmonary œdema and hypostatic bronchopneumonia. In this series therefore the maternal mortality rate was 0.26%.

Total Fetal Deaths—9 in 379 Fetuses

| | |
|---|---|
| Complete abruptio placenta with dead fetus | 2 |
| Ruptured uterus with dead fetus | 2 |
| Central placenta prævia and prematurity | 1 |
| Fetus dead before operation (large stillborn) | 1 |
| Congenital absence of kidneys | 1 |
| Toxæmia and placenta prævia | 1 |
| Fetal atelectasis | 1 |

From this series it is seen that five fetuses were dead before surgical interference; one had congenital absence of the kidneys, leaving three that did not withstand the surgical procedure. This is 0.8% fetal death that could possibly be attributed to the anæsthetic or the surgical procedure.

The total number of premature infants (five pounds or less) was eleven. One premature died and in this instance the Cæsarean was performed for central placenta prævia.

The Time Factor

| | *Minutes* |
|---|---|
| Average induction time of anæsthesia | 3½ to 4 |
| Shortest induction time of anæsthesia | 1½ |
| Longest induction time of anæsthesia | 15 |
| Average time from start of anæsthetic until infant was delivered | 9 to 10 |
| Shortest time from start of anæsthetic until infant was delivered | 3 |
| Longest time from start of anæsthetic until infant was delivered | 32 |

### Comment

*The infant.*—Combining low toxicity, rapidity of action and high oxygen content, cyclopropane, using this technique, has proved itself to be an ideal agent for Cæsarean section. Particularly is this true for the welfare of the infant. In this series, there were eight infants only who appeared sluggish and required some resuscitative measures. The remaining infants showed no respiratory depression, their colour was good and spontaneous respiratory activity on delivery was the rule. The greatest hazard to prematures is prematurity itself, followed closely by anoxæmia. It has been our experience that prematures do exceedingly well with cyclopropane.

*The mother.*—The superiority of cyclopropane lies in the contentment of the patient under general anæsthesia as compared with regional analgesia, and in the unquestionably smooth postoperative course of these patients with their comparative freedom from complications. During the operation freedom from cyanosis, excellent uterine tone with little bleeding, and ease in carrying out additional procedures are invariably the rule. Postoperatively, early recovery, little vomiting and absence of distension and early comfortable ambulation are confidently expected and are rarely absent. Particularly where shock is present cyclopropane has been found to be the ideal anæsthetic.

SUMMARY

This is a review of 378 consecutive Cæsarean sections using general anæsthesia with cyclopropane with one maternal death which cannot truly be ascribed either to the operation or the anæsthetic, and a net loss of three infants.

An indispensable member of the operating team is a fully qualified and competent anæsthetist.

I wish to acknowledge the help given by Dr. B. C. Leech, Director of Anæsthesia at the Regina General Hospital, and by Dr. M. W. Bowering, Anæsthetist, in the preparation of this paper, and to thank the members of the medical staffs of the Regina General Hospital and Regina Grey Nuns' Hospital for their kindness in permitting the use of the statistical material here presented.

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RÉSUMÉ

Communication portant sur l'emploi du cyclopropane comme anesthésique dans 378 césariennes. Mortalité maternelle: 1; fœtale: 9, dont quatre enfants morts avant l'opération et un souffrant d'absence congénitale des reins. De 11 prématurés, 10 ont survécu. Avantages pour la mère: anesthésie complète, conservation du tonus utérin, peu de désagréments post-opératoires. Pour l'enfant: absence de dépression de la respiration, particulièrement remarquable dans le cas des prématurés. PAUL DE BELLEFEUILLE

## B.C.G.—A REVIEW

**Lillian E. Martin***

*Calgary, Alta.*

WE owe the development of B.C.G. to Drs. Calmette and Guerin. They first began their work of attenuation in 1906, using a virulent bovine strain. By 1921, after interruptions due to the war they were applying this now thoroughly attenuated culture to the protection of cattle and in 1921 it was first given to infants by Weill-Hallé of Paris. The first serious setback to its use came in with the Lubeck disaster in 1929, when 14 infants died and 70 became seriously ill with tuberculosis, in a series of 252. It was concluded however that the tragedy was not caused by the B.C.G. itself, but rather by carelessness in the laboratory which permitted of the mixing up of virulent and avirulent cultures. Since 1931, B.C.G. vaccine number 423 has been developed and found to be satisfactory. This development required constant effort and meant subculturing in rotation on specified media — bile potato, Sautan's medium, glycerine broth, glycerine potato, etc. The criterion of potency or virulence is checked by the number of tuberculous nodules produced by guinea pig injection.

The vaccine is prepared by separating the culture of desired virulence from the medium by filtration. This is dried and pressed into a solid cake, kept sterile and stored in a moist environment. When needed the required amount of cake is emulsified with Sautan's medium and distilled water and the resulting vaccine is said to be good for forty odd days — though for safety's sake five days is suggested for maximal storage.

For ideal results the following factors should be considered. (1) Environment — *i.e.* intelligence and co-operation of parents. (2) Exposure conditions—*i.e.* frequency of exposure, amount of sputum being expectorated, number of organisms in sputum, etc. (3) Other factors may be age or racial differences.

### OBSERVATIONS IN VARIOUS COUNTRIES

*Sweden.*—There is a movement in Sweden to adopt B.C.G. vaccination of every tuberculin negative member of a community.

*Denmark.*—Jensen has noticed that virulence of B.C.G. varies but even in its most virulent form it has never given rise to a progressive lesion. The variation has been a nuisance and Jenner and his colleagues claim to have a technique which has ensured constant virulence of vaccine over several years.

*Scandinavian countries—in general.*—A great deal of work has been done with B.C.G. during the years of the second Great War and the views on its efficacy continue to be much more optimistic than in Britain or the U.S.A. The common experience has been that the vaccine is harmless and highly effective. The average tuberculin sensitivity following vaccination averages 4 years but it may disappear after 1 year.

There was no move towards mass vaccination until the Nazis tried to suppress its use, then, particularly in Norway, the number of vaccinations sky-rocketed and where necessary B.C.G. went underground. The number vaccinated in 1940 was 674 while about 23,000 were done in 1945. The National Tuberculosis Association of Norway is encouraging a law for *obligatory* vaccination (B.C.G.) of every tuberculin negative reactor in the eight public school grades and

* Supervisor of the Laboratory of the Calgary Associate Clinic.

suggests *voluntary* vaccination of every negative reactor between the ages of 15 and 50.

*Brazil.*—B.C.G. is widely used in federal districts. Of 23,082 babies born in 1941, 44% were vaccinated; 21 of 53 babies not vaccinated became infected—7 died; 10 of 48 babies who were vaccinated became infected—1 died.

*Soviet Russia.* — Ten newborn infants in Moscow were vaccinated in 1927; 2,981 newborn infants in Moscow were vaccinated in 1940; every newborn infant in Moscow was vaccinated in 1941.

Mass vaccination of newborn in Russia is considered to be one of the most important antituberculous measures. Widespread use of the vaccine in distant Russian villages is sometimes hindered by the limited life of the vaccine. Some authors claim it is possible by increasing the quantity given to secure the required dose of bacilli for effective vaccination.

Mortality from tuberculosis was investigated in Moscow in a group of 57,000 infants in 1938. There was found to be a significant reduction in the vaccinated groups in the first two years of life. Infant mortality from T.B. fell by 40% between 1933 and 1940; during this time the number of vaccinations carried out rose greatly.

| *Moscow* | | *Leningrad* | |
|---|---|---|---|
| 1933 ..... | 3,000 | 1933 ..... | 5,000 |
| 1940 ..... | 103,000 | 1940 ..... | 48,500 |

In Russia a study was made of lymphadenitis among 2,700 infants and found to be present in 2.5% in towns where mass vaccination was carried out. In several large towns vaccination was not followed by this complication. It seemed to occur only where the "Paris" strain of bacilli was used for making the vaccine. When the strain was changed cases of adenitis were no longer seen. In 1,973 cases of lymphadenitis observed in vaccinated infants contact with T.B. was found in 23.

The conclusion of the study was that the disease (lymphadenitis) is benign and is not an indication for abandoning vaccinations.

*United States.*—Here 1,565 Indians have been vaccinated, in various tribes from Texas to Alaska. There have been no untoward or general reactions, no abscess or ulceration of regional lymph nodes. It is generally agreed there is no substitute for proper public health measures to prevent infection with T.B. The degree and rate of development cannot be measured by any known test or its duration be determined. The further need for research in this field is obvious and is being accepted as a responsibility by the Tuberculosis Control Division of the U.S.A. Public Health Service.

*Canada.*—Interest in the use of B.C.G. is growing. Much credit is due to Dr. Armand Frappier, Director of the Institute of Microbiology and Hygiene of Montreal for his work during the past 20 years in preparing and promoting the use of B.C.G. Quebec is apparently the pioneer province in its use. Dr. R. G. Ferguson of Saskatchewan is credited with a splendid clinical study of B.C.G. In the past unfortunately the extensive work done has not been as well documented as Dr. Ferguson's.

2,042 nurses in Saskatchewan Hospital were subjects in 1934-43.

Of 1,005 non-reactors vaccinated, 9 acquired manifest T.B., approximately 9%.

Of 759 non-reactors not vaccinated, 29 acquired manifest T.B., approximately 4%.

Of 278 positive reactors not vaccinated, 3 acquired manifest T.B., approximately 1.2%.

Difference in percentages for vaccinated and non-vaccinated negative reactors is statistically significant. A separate study was made of graduate nurses and nursing assistants of the three Saskatchewan sanatoria because they were in most direct contact with the disease.

Of 203 non-reactors vaccinated 5 acquired manifest T.B., approximately 2.45%.

Of 113 non-reactors not vaccinated 18 acquired manifest T.B., approximately 15.9%.

Of 293 positive reactors not vaccinated 11 acquired manifest T.B., approximately 3.7%.

From these results it was concluded that B.C.G. is not a 100% prophylactic but it provides considerable protection and is safe. Lesions were less extensive in the vaccinated negative reactors than in the non-vaccinated. The serious excessive incidence of T.B. among nurses and sanatorium employees who did not react to tuberculin when they entered the environment during 1930-38 was not present after vaccination was begun in September 1938. Dr. Ferguson's work and reports have been so conclusive that the use of B.C.G. has been adopted by the Canadian Tuberculosis Association.

*Three methods of administration.* — (1) By mouth—only popular in France. (2) Subcutaneous—not popular as it may cause violent reaction with abscess. (3) Intercutaneous—

the preferred method. A small cold abscess may appear which will usually soften and open spontaneously. In such a case the formation of a scar is possible. This scar may show an examining doctor later on that the tuberculin positive child has undergone a B.C.G. vaccination, a fact that may have been forgotten by the parents.

Dr. Ferguson suggests obtaining the vaccine from Dr. Frappier via air mail, always using it while it is fresh.

It is important to remember that persons to be vaccinated should be really tuberculin negative. A Mantoux test up to the highest dose must be done. If tuberculin-positive persons are vaccinated the risk of unpleasant local reactions at the site of vaccination is very great. Tuberculin tests should be done 5 to 7 weeks after vaccination. Revaccinate negative reactors and repeat their tuberculin test 5 to 7 weeks after revaccination. Tuberculin test once yearly and revaccinate when found to be negative.

X-ray the chest immediately after tuberculin is positive, every three months for one year, and every six months for the next two years. X-ray the chest on revaccinated persons with the same routine as in those positive with first vaccination.

The vaccine obtained from Montreal is prepared for oral use. Each 2 c.c. vial contains 10 mgm. of B.C.G. and can be diluted for intercutaneous injection. 1 to 2 c.c. vial is diluted with 10 c.c. sterile normal saline, (each c.c. of dilution will contain 1 mgm. B.C.G. and each 1/10 c.c. of solution will contain 0,1 mgm. B.C.G.).

*Dose.*—Inject 1/10 c.c. of dilution intercutaneously as in a tuberculin test, forming a wheal on upper arm or thigh and a similar dose in same manner about 1″ from previous site. Total dose then is 2 mgm. B.C.G.

By so dividing the dose and injecting at two sites, ulceration is minimized. It is suggested now that the dose be divided into three injections. Dr. Frappier advocates multiple injections. To avoid ulceration the softened abscess should be punctured (not opened) with a syringe and needle. This is not always necessary but it helps prevent formation of scar; healing is usually the rule within a few weeks.

The following facts may have some bearing on failures in use of B.C.G. (1) B.C.G. in the human is caused by cross-immunization of attenuated bovine strain of tubercle. (2) Perhaps Calmette and Guerin went too far in the attenuation of virulent bovine strain since to them harmlessness was the main requisite. If so, less attenuated strains found to be harmless in bovines might be resorted to. (3) Infection in humans as a rule is by human organisms.

*In Alberta.*—At present B.C.G. is not being used on nurses in training at the Calgary General Hospital. At the Holy Cross Hospital in Calgary they started using it last September and to date 135 nurses have been inoculated. It is being used by Dr. Davidson at the General Hospital in Edmonton and many negative reactors were vaccinated at the Oliver Mental Institute. It is being used on all nurses and nurses aids at the Central Alberta Sanatorium entirely on a voluntary basis; there is the rare objector. There are no figures available yet for Alberta statistics but to date there have been no local or general reactions and it is felt quite reasonable to add B.C.G. vaccination to our preventive program.

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## RÉSUMÉ

Revue de la préparation du B.C.G. et de son usage à l'étranger. On reconnaît généralement, dans un grand nombre de pays européens, son innocuité et son efficacité, relative mais réelle. Au Canada, son usage est en voie de se répandre, grâce aux efforts de M. Armand Frappier à Montréal et de M. R.-G. Ferguson dans l'Ouest. Le B.C.G. se donne par injections intracutanées multiples, aux seuls sujets dont la tuberculinoréaction est négative. Celle-ci devient positive dans un espace de 5 à 7 semaines; sinon, la re-vaccination s'impose. On doit répéter l'épreuve à la tuberculine au bout d'un an, et re-vacciner s'il y a lieu.

PAUL DE BELLEFEUILLE


The heaviest head of corn hangs its head lowest.—Gaelic Proverb.

# CASE REPORTS

## A CASE OF PRENATAL (CONGENITAL) SYPHILIS

**Ben Kanee, M.D.***

*Vancouver, B.C.*

Modern medicine has made tremendous strides in the prevention and treatment of prenatal (congenital) syphilis. 1943[1] marked the beginning of a new era in the ever-present struggle to eradicate prenatal syphilis. The introduction of penicillin has resulted in a general unanimity of opinion amongst leading syphilologists[2] that, despite the present-day experimental status of penicillin, it has provided mankind with the means of eliminating entirely this tragic form of syphilis. This goal is possible of attainment if we maintain a strong index of suspicion in regard to syphilis and if blood tests are used at regular intervals as a standard procedure in prenatal examinations.

It is most important to establish the diagnosis early in syphilis of pregnancy. Should the diagnosis not be established during the prenatal period, it is still posible to detect syphilis of the newborn early enough to institute proper and adequate therapy if a cord Kahn is performed in all newborn. Had this been taken in the following case, a life might have been saved. The great importance of this from a public health point of view and the simplicity and ease in carrying out this diagnostic measure, coupled with the readily available drugs to treat and possibly cure early prenatal syphilis, would suggest it as timely to report the following tragic case.

Male baby, R.M., aged five weeks, was admitted to the Infants' Hospital on August 8, 1947. The entrance complaints were constipation, refusing part of feedings, apparent abdominal pain, increasing jaundice and passing concentrated urine of four days' duration and regurgitation since birth.

The child was born June 27, at the Vancouver General Hospital by premature spontaneous delivery. At birth the infant was fetal age of seven months. Birth weight was 5 pounds, 1 ounce. There was no history of breast feeding and the child did well on evaporated milk up until August 4. Siblings, ages 9, 7½ and 6 years respectively, all alive and well.

*Physical examination.*—Weight on admission was 7 lb., temperature, 99° F. Splenomegaly and hepatomegaly were present. The abdomen was distended and rigid and the skin was icteric. There was a confluent as well as a discrete maculopapular erythematous rash on the thighs and ankles on the flexor surfaces and over the elbows.

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The result of the examination of the blood was as follows: Hgb. 30 to 40%, red blood cells 1,220,000, white blood cells 36,000, polymorphonuclears 36%, staff cells 8%, lymphocytes 42%, monocytes 1%, myelocytes 1%, myeloblasts, lymphoblasts and prolymphocytes 10% and disintegrating cells 2%. Urinanalysis: specific gravity 1.018, albumen 3 plus, sugar and acetone negative, white blood cells 2 plus, granular casts 2 plus and bacteria 3 plus. The nose and throat swabs were negative. The culture of the stools was negative.

*Autopsy findings* (Dr. J. E. McDonagh).—The body was that of a well developed, well nourished male infant, five weeks old. On external examination the pupils were seen to be equally dilated to 2 mm. in diameter. The sclera and skin surface showed a marked degree of icteric tinting. The whole body had a moderately œdematous appearance. A minor degree of rather bluish mottling was seen over the flexor surfaces of the thighs and legs as well as over the region of the sacrum. These areas did not appear to be raised above the general body surface nor was there any induration noted.

*Macroscopic findings.*—Both right and left lungs appeared to be of normal size. However, the gross surface was rather variegated and this variegation was sharply demarcated, there being irregular areas, some yellowish-white and some pink, some dark red and purple in colour. These variegated areas were also seen on sectioning the lung tissue. The general cut surface was rather moist exuding a rather yellowish discharge. The purplish red areas were interspersed over the cut surface and presented a more dense appearance than did the more lightly coloured areas.

The peritoneal cavity was of note in that it contained 10 to 15 c.c. of a yellowish clear fluid. Furthermore, there was a marked degree of hepatomegaly and splenomegaly. The liver appeared to be about one-third greater than the normal size. The biliary tract was patent throughout. The cut surface of the liver was of a yellowish green colour, quite firm in consistency and of a rather greasy nature. The gastro-intestinal tract and pancreas appeared normal. The spleen was enlarged to approximately three times. The cut surface was soft and rather pulpy and of a purplish red colour. The adrenal glands and genito-urinary tract showed nothing abnormal except a right encysted hydrocele containing approximately 4 c.c. of a clear yellowish fluid.

*Microscopic findings*: *Lungs.*—Sections showed the alveoli to be well expanded. However, there were numerous large areas where the alveolar spaces were packed with red blood cells. Many meconium-like bodies were also seen in the alveolar spaces along with large macrophages. Some hæmorrhagic areas were seen to have an exudative element, in the presence of variable quantities of muco-staining granular coagulum. The picture presented was consistent with multiple discrete, intra-alveolar hæmorrhages.

*Liver.*—Sections stained with hæmatoxylin and eosin were scarcely recognizable as liver, there being such an extensive morphologic change. The lobular structure was completely disorganized and the hepatic cells had completely lost their cord-like configuration. There was an over-all increase in fibrous tissue to such an extent that the fibres separated the individual hepatic cells. The hepatic cells themselves were markedly atrophic with granular cytoplasm. The nuclei were often pyknotic or undergoing chromatolysis. In fact, many areas which under low-power appeared to be infiltrated with inflammatory cells, under high-power were seen to be naught but pyknotic nuclei and those undergoing chromatolysis.

Sections stained with Levaditi's stain revealed the presence of spirochetes.

The kidneys and pancreas showed only post mortem degeneration.

The testes showed an increase in the number of interstitial cells seen as compared to that found in the adult state.

In summary, the pathological findings were: congenital syphilitic hepatitis and massive intra-alveolar hæmorrhages due to syphilis.

Subsequently additional history came to light. The father acquired primary syphilis in November, 1945. The mother was diagnosed syphilis acquired early latent seropositive in February, 1946 and lapsed from treatment after receiving but one injection of an arsenical.

### COMMENT

Every textbook on obstetrical medicine points to syphilis as one of the main causes of prematurity. A positive cord Kahn does not spell syphilis in the presence of an apparently healthy child, as it may be due to the placental transfer of maternal reagins. A positive cord Kahn, however, does definitely place a responsibility on the attending physician to establish or rule out syphilis. The use of quantitative blood Kahns is of great help, as a sustained or rising titre in successive tests at two to twelve weeks after birth in this type of case would spell syphilis. Other aids are roentgenographic findings of involvement of the epiphyseal ends of the long bones and clinical evidence of the disease such as snuffles, rash (maculo-papular to bullous lesions on the extremities and about the orifices) and an enlarged liver and spleen. The appearance of myeloblasts, lymphoblasts, prolymphocytes and nucleated red blood cells in the blood smear may be accounted for by the extra-medullary hæmatopoiesis in the liver and spleen due to prematurity (7 months) and to the stimulation of these organs by the syphilitic infection.

This infant was seen by the author two hours before its death. A diagnosis of syphilis was not established on clinical grounds but it was felt that syphilis had to be excluded and with this in mind ascitic fluid was withdrawn from the scrotum as a simple procedure and examined for the presence of spirochætes. A darkfield examination of a centrifuged specimen of this ascitic fluid was positive for spirochæta pallida and a quantitative Kolmer complement fixation test on this fluid was positive, 64 Kolmer units. A quantitative Kahn test on the infant's blood was positive, 320 Kahn units, and the blood complement fixation test was also positive. In retrospect it is felt that a cord Kahn taken at birth in the above case would possibly have aided in establishing the diagnosis and that modern therapy might have saved a life.

### SUMMARY

1. A plea is made for the routine use of blood tests as part of the regular prenatal care, as the means of early diagnosis and treatment of syphilis of pregnancy and the prevention of syphilis of the newborn.

2. A further plea is made for the routine use of the cord Kahn as an aid in the diagnosis of prenatal (congenital) syphilis.

3. A case of prenatal (congenital) syphilis is reported where a positive darkfield and Kolmer complement fixation were obtained on the ascitic fluid.

Appreciation is expressed to Dr. John Piters, pædiatrician, for permission to report this case.

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## A BLEEDING URETHRAL VARIX

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*Calgary, Alta.*

The writer has never heard of or come across a bleeding varix within the urethral channel of the degree presented by the case to be described. The following case was thought of sufficient interest to report.

A male 32 years of age was referred to me for examination for painless bleeding from the penis, not hæmaturia, but a steady ooze of blood out of the urethral meatus. The bleeding had began two weeks previously. It lasted three days, ceased, and then recurred two days before examination to continue till the day I saw him. He was a healthy looking young man. There was no history of venereal disease or disease of the genito-urinary system. The physical examination except for the bleeding was essentially negative. Examination of the penis revealed a normal urethral meatus. Palpation of the penis showed no abnormality. The testes were normal to palpation. Rectal examination revealed a normal prostate. The bleeding had no relation to sexual intercourse. He is a happily married man. There was no history of trauma to the penis. There was no history of bleeding from the nose or elsewhere. There was no frequency, nocturia or dysuria. When not bleeding he stated urinalyses were always normal.

*Past history of urethral bleeding.*—He first had urethral bleeding in 1927 at the age of 11 years for no apparent reason. This lasted two weeks and then ceased. The family doctor attributed this to trauma while at play but the patient denied this. He was free of any bleeding until 1937 when again for no apparent reason the urethral bleeding started. It lasted two weeks. He lost so much blood that he was put in a hospital for a week. He was not urethroscoped.

In 1938 he had another bout of bleeding. This was the most severe to this date. He stayed at home in bed two weeks and spent another two weeks in the hospital. He lost so much blood that his doctor was considering giving him a blood transfusion but did not do so. He was cystoscoped twice in the hospital and three or four times in the doctor's office. Pyelograms were taken but no abnormality was found in the upper urinary tract.

The urethra apparently also was examined but no abnormality found. In 1939 a bout of bleeding of mild degree lasted a week during which time he stayed at home in bed. He did not consult a doctor as no cause could ever be found for the hæmorrhage.

He joined the Air Force in 1940 and volunteered his history of urethral hæmorrhages. The medical examiners apparently put little credence in this. That same year bleeding occurred. It lasted ten days, during which time he was kept in a small station hospital but was not cystoscoped. He was out of the hospital only three days when the bleeding recurred so he was sent to a larger centre for urological consultation. Here he was hospitalized for 33 days during which time he bled most of the time. He was cystoscoped about four times but no cause was found for the bleeding. He was discharged from the Air Force due to the hæmorrhages.

In 1946 some slight bleeding lasted three or four days but he continued to work.

Many clots were passed with these bouts of bleeding. At times the bleeding would occur during sleep. When staying at hotels he found this most embarrassing. It was difficult to explain away bloody sheets. When the bleeding commenced he took to wearing a condom to prevent soiling of his underwear and trousers but he could never tell when the bleeding would start. He felt his usual well being during these hæmorrhages. He had undergone at least twenty cystoscopic examinations and was getting a bit fed up with these procedures.

On April 28, 1948 an F. 24 panendoscope was easily passed. The bladder interior was normal. The whole length of urethra was examined. The prostatic urethral mucosa had an appearance of laxity, almost redundancy, particularly around the bladder neck but was otherwise normal. The verumontanum appeared normal. About 1½ inches distal to the external bladder sphincter on the left urethral wall was a very pale bluish discoloration, irregular in outline, about ¼ inch long by ⅛ inch wide and from one point a slight ooze of blood was seen. In tiny spots the bluish colour was more pronounced as if here the varix was much closer to the surface, giving one the impression as if covered here only by a single layer of urethral mucosal cells or none at all. The area of the varix was lightly fulgurated. The bleeding ceased. It is thought that it might recur and another light fulguration may be necessary.

SUMMARY

A case of a bleeding urethral varix or it may be a hæmangioma is presented with a long history of bouts of hæmorrhages. It is hoped that the fulguration will cause sufficient scarring over the varix to prevent future bleeding.

The world today, as never before, stands in need of balanced, well-informed minds that are consumed with a desire to know what is going on and why. Men so endowed will be intolerant of the ills of society; they will seek a remedy and will spend themselves in trying to apply it. The course is a hard one. "The Preacher" has told us that he who increaseth knowledge increaseth sorrow; but the sorrow that comes from knowledge of the sufferings of society turns to joy when it is translated into service. Service must be the watchword, and in service the awakening of dull and sleeping minds must not be forgotten.—Mervyn Archdall.

## DIFFICULTIES IN DIAGNOSIS BETWEEN TUBERCULOSIS AND LOEFFLER'S SYNDROME

**C. S. Barker, M.D., F.R.C.P.[C.] and J. A. Fownes, M.D.**

*Montreal, Que.*

Numerous reports have appeared in the literature, particularly in the last ten years, concerning transitory pulmonary infiltrations, and considerable emphasis has been placed on the problem of differential diagnosis between pulmonary tuberculosis and the type of transitory infiltration associated with eosinophilia. It is felt that a useful purpose may be served in

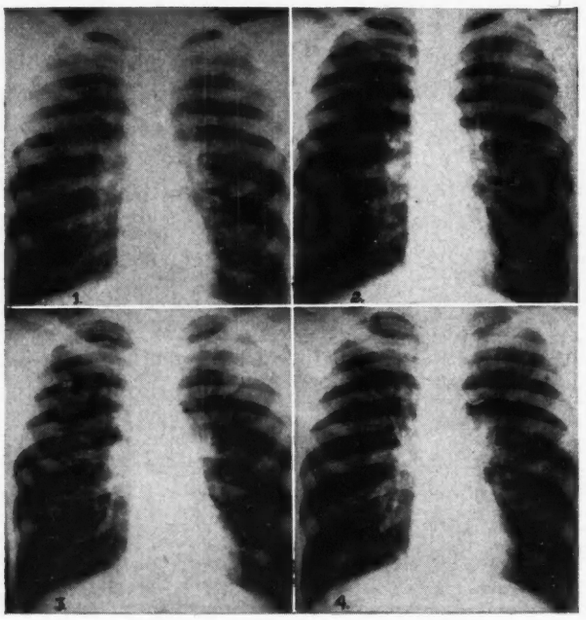

**Fig. 1.**—27-1-47.—Area of infiltration left upper lung field. **Fig. 2.**—26-3-47.—Infiltration is almost double in size. Tuberculosis cannot be entirely ruled out. **Fig. 3.** — 12-4-47. — Increase in lesion both sides. Opinion — Active pulmonary tuberculosis. **Fig. 4.** — 9-6-47.—Focal deposits in left upper lobe have entirely regressed. We must still consider the possibility of tuberculosis.

reporting another case, in which difficulty in diagnosis was experienced and in which the factors involved in the differential diagnosis may be presented and summarized.

A youth of 18 years was admitted to the Royal Victoria Hospital on January 24, 1947. Briefly his history was that of recurrent attacks of asthma since the age of 6 years. A particularly severe attack began on January 12, 1947, and persisted until the admission became necessary.

From the date of entry into hospital until early in May, despite symptomatic therapy and attempts at elimination of possible allergens, etc., the patient continued to have asthmatic attacks of varying degrees of severity. On April 25, deep x-ray therapy to his chest

was instituted and continued until May 21. During this period improvement, which may have been due to the x-ray therapy, took place.

For purposes of the report details of the case, other than those listed below, will not be elaborated. It may seem that x-ray and bacteriological reports are present to the point of monotony but this is intentional, and will serve to emphasize the difficulties experienced in reaching a final conclusion as to diagnosis.

The x-ray, clinical and laboratory findings are shown in the table at the foot of this page.

In reading the reports tabulated above one is impressed by the obvious state of doubt in the mind of the radiologist who, at times suggested strongly, and at other times cast serious doubt upon the diagnosis of tuberculosis. The temptation to establish a final diagnosis is almost too strong when the bacteriologist finds acid-alcohol fast rods of questionable type. The hæmatologist too, on his first study, queries tuberculosis.

The authors of this report, after prolonged observation of the case, finally came to the conclusion that the infiltration was probably not tuberculosis but was probably an infiltration of the Loeffler type. It would seem to be of value at this point to set down in table form those factors in a case which favour a diagnosis of tuberculosis and those which favour Loeffler's syndrome (see next column).

| *Favoring Tuberculosis* | *Favoring Loeffler's Syndrome* |
|---|---|
| 1. Family or contact history. | History of asthma or other allergy. |
| 2. The clinical mode of onset of tuberculosis—fatigue, loss of weight, night sweats, etc. History of hæmoptysis or previous tuberculosis. | Recent or present allergic episode. |
| 3. Physical examinations—there may be suggestive localized pulmonary signs. | Physical examination—there may be the generalized pulmonary signs of asthma. |
| 4. X-ray examination — there may be evidence of cavitation; upper lung field location; tendency to persist in one area for at least several weeks; tendency to leave residual scarring. | X-ray examination — the lesion may be anywhere in the lung; tendency to wax and wane in different parts of the lung fields; tendency to clear in shorter periods; there may be residual scarring. |
| 5. Tuberculin test; probably positive sooner or later. | Tuberculin test—if negative this helps to eliminate tuberculosis. |
| 6. Hæmogram; there may be an increase in the sedimentation rate with change in the lymphocyte-monocyte ratio. | Hæmogram; the sedimentation rate may be increased. There is a tendency to eosinophilia which may be as high as 60% or even more. |
| 7. Sputum or stomach washings: acid fast bacilli should be present to establish a definite diagnosis. | Sputum or stomach washings: acid fast bacilli absent after continued search. |

| *Date* | *Mantoux test* | *X-ray* | *Hæmogram* | *Bacteriology* | *Course* |
|---|---|---|---|---|---|
| 25–1–47 | | Area of infiltration left upper lung field. | | | |
| 29–1–47 | | Soft area of infiltration appearance suggestive of Tbc. | Sed. rate W.B.C. 37; 10,-700; Eosin. 17; Polys. 66; Lymph. 8; Mono. 8; Neoplasm and Tbc. should be excluded. | Sputum-mixed growth of normal flora. | Severe asthma |
| 10–2–47 | | Almost complete regression. Loeffler's syndrome possible. Tbc. must not be entirely eliminated. | | Sputum culture no Tbc. | Improved |
| 19–2–47 | 1/100 neg. | No appreciable change; must be regarded as Tbc. until proved otherwise. | | Sputum culture heavy growth of enterococci. Lancefield Group D. | |
| 26–2–47 | | Slight reduction in size and sharper delineation. Opinion—Tbc. left upper lobe. | W.B.C. 7,700; Stab. 10; Poly. 47; Eosin. 22; Lymph. 19; Mono. 2. | Stomach washing smear—no Tbc. | Severe asthma |
| 3–3–47 | 1/100 neg. | Area infiltration left upper lobe larger—also small area of infiltration right upper lobe. | | | Improved. |
| 25–3–47 | 1/100 neg. | Infiltration is almost double in size. Tbc. cannot be entirely excluded. | W.B.C. 12,600; Stab. 6; Poly. 53; Eosin. 17; Mast. 2; Lymph. 17; Monos. 5. | Gastric washing smear. 3-5 questionably acid-alcohol fast rods not characteristic of morphology. Culture—negative Tbc. | |
| 30–3–47 | | Tomogram—a parenchymatous lesion. Some small areas of rarefaction left upper lobe. | Sed. rate 23; Stab. 2; Poly. 73; Eosin. 8; Lymph. 6; Monos. 11. | | Severe asthma |
| 7–5–47 | | Considerable regression, more of strand appearance. | | Stomach washing smear—Neg. for Tbc. | Improved. |
| 9–5–47 | | Focal deposits in left upper lobe have entirely regressed. Must still consider possibility Tbc. | Sed. rate 10; Stab. 11; Poly. 74; Eosin. 3; Lymph. 9; Monos. 3. | | Much improved |

In the differentiation of infiltrations of this type other pulmonary conditions should not be forgotten, *e.g.*, malignancy, fungus infections, atelectasis and pulmonary infarction.

No attempt has been made to review the literature or to discuss the etiology or pathology of Loeffler's syndrome. One of the authors (C.S.B.) reviewed the literature of this syndrome in 1939.[1] An excellent recent discussion with bibliography is contained in the report of Peirce *et al.*[2]

*Progress note.*—An x-ray taken in February, 1948, shows further regression of the parenchymal changes. The Mantoux test was still negative, 1-100, in May, 1948.

SUMMARY

The purpose of this article is to stress the importance of differentiating between pulmonary tuberculosis and Loeffler's syndrome. A case considered to be of the latter type is presented illustrating the difficulties in differential diagnosis.

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## INIENCEPHALUS

**D. F. Osborne, M.D.**

*Winnipeg, Man.*

In 1939, a complete review of the literature by Brodsky revealed 57 reported cases of iniencephalus. Paterson in 1944 reported 4 cases of this rare fetal abnormality. The history and various interpretations of this abnormality have been thoroughly covered by previous papers. All cases present a triad of features accepted by all authors: (*a*) fetal retroflexion; (*b*) deficiency of the occiput; (*c*) rachischisis of variable extent. The abnormality is subdivided into iniencephalus clausus with no meningocœle and iniencephalus apertus with a meningocœle.

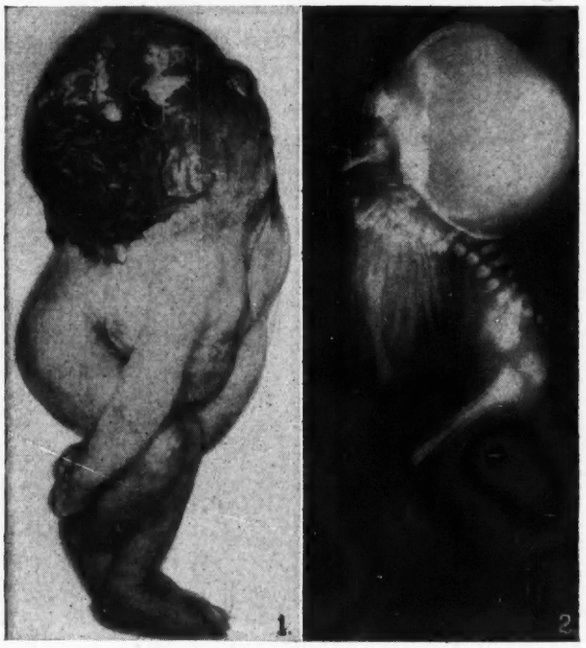
The cases here reported represent both subdivisions.

### CASE 1

The patient was a nulliparous woman, aged 23, married 2 years. Past history was uneventful. The patient consulted an obstetrician on September 15, 1945, the expected date of delivery being April 27, 1946. No history of infection in the early weeks of pregnancy. The pre-natal history was normal up to March 5, 1946, when marked polyhydramnios and peripheral œdema were noticed. A flat film of the abdomen was reported on as follows: "There is a single fetus with the head high in the abdomen. There is extreme extension of the spine, particularly in the cervical and upper thoracic regions. There is a strong suggestion of a wide defect posteriorly in the lumbar region. The legs are directed downwards and the knees are flexed. A fetal abnormality seems highly probable—possibly a large meningocœle."

The patient was admitted to hospital April 2, and the membranes ruptured artificially at 10.30 a.m. the next day. Active uterine contractions were established at 8.00 p.m. April 3. The fetus presented by the breech and delivered up to the umbilicus with no difficulty. The body would deliver no further and in view of the x-ray diagnosis of a possible meningocœle, an attempt was made to perforate the mass anteriorly. When bone was encountered, the body and head were rotated posteriorly and the fetus delivered face-to-pubes. It breathed 6 to 8 times, voided and then expired. The fetus was a male, weighing 4 lb. 10 oz. and had extreme retroflexion of the head, with no apparent meningocœle.

As the fetus was presented to the Department of Anatomy, University of Manitoba, no post-mortem was performed. The following is a report on the post-partum radiography of the fetus:



"The sacrum, pelvis and extremities are well formed and there are well formed vertebral bodies for the lower four lumbar vertebræ, although their posterior portions are open. The cervical and thoracic vertebræ are extremely malformed and there is an extreme degree of extension, with its apex near the upper thoracic region. The occipital bone lies in close relationship with the vertebral column downward as far as L. 3 and there is probably a mid-line defect in the occipital bone. The skin which is reflected from the back of the skull is continuous with the skin over the sacrum. The head looks upward and forward. This appears to be a typical case of iniencephalus."

### CASE 2

The patient was a 2nd gravida, aged 30, married in 1939. She consulted an obstetrician on June 6, 1947, the expected date of delivery being January 22, 1948. First child born in 1941 weighed 7 lb. 13 oz. The patient stated that labour lasted 32 hours and was very difficult. From 1943 she had a vaginal discharge and lower abdominal pain. In 1945 she had cervicitis with blood stained discharge. Conization of the cervix per-

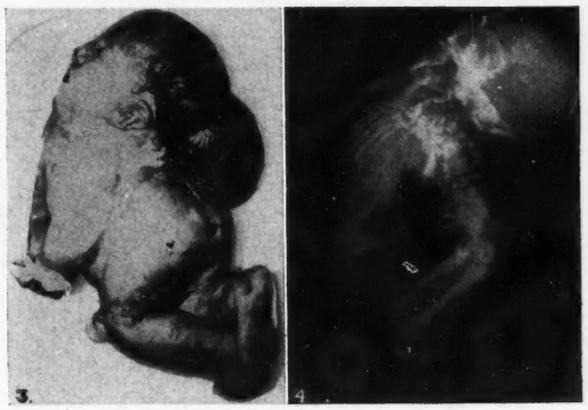
formed December 3, 1945, in the Winnipeg General Hospital.

No evidence of infection in the early months of present pregnancy. On June 6, her blood picture showed: red blood cells 3.95 million. Hæmoglobin 69%; colour index 0.9. On December 19, her hæmoglobin was 73%. Because of evident polyhydramnios and small fetus, x-ray films were taken and reported on as follows:

"Single fetus in about 7th month of pregnancy with marked fetal deformity and aplasia of the vertebral column. Head is extended. These features are considered evidence of a severe congenital abnormality. Hydramnios is also present."

On January 2, 1948, her blood was: red blood cells 4.52 million and hæmoglobin 81%. She was admitted to hospital January 4 and at 9.30 a.m. the next day the membranes were ruptured and considerable liquor amnii escaped. The breech was presenting. At 4.38 p.m. January 7, a female fetus, weighing 5 lb. 10 oz. was delivered stillborn with no difficulty. There was a large meningocœle at the neck with extreme extension of the head.

The following is a report on the post-mortem radiography of the fetus: "There is extremely gross malformation of almost the entire vertebral column and there are multiple anomalies of the ribs. The neck is acutely extended, with the occiput attached by soft tissues to the lumbar vertebræ A large defect is present



3. 4.

in the occipital bone and there is a large soft tissue shadow about 7 cm. in diameter, presumably a meningocœle, which extends downwards as far as the buttocks. Impression: Iniencephalus associated with cranium bifidum."

*Post mortem findings.*—The head is in extreme extension. No neck is demonstrable. The chin merges into a protruding pigeon chest. The umbilicus contains herniated and adherent small bowel. The limbs are normal. The back is acutely angulated to the left as well as the lumbo-dorsal curve being intensified. Brain is present and grossly normal. The foramen magnum is enlarged measuring 27 mm. in lateral diameter and 37 mm. in antero-posterior diameter (including defect). Arising from the posterior surface is a triangular defect with the base at the foramen magnum and apex pointing posteriorly. Maximum depth of the defect is 14 mm. At the level of the foramen magnum is a large meningocœle measuring 10 cm. in diameter and containing bloody fluid and some free autolyzed cerebellum. The entire dome of the left diaphragm is absent. The entire stomach, spleen, tail of the pancreas, left adrenal and upper pole of the kidney are contained in the left pleural space. The dorsal and ventral segments of the embryological head of the pancreas are still separate and ununited. There are two separate and identical spleens united by a common artery.

*Gross anatomical diagnosis.*—(1) Stillborn female, term fetus with multiple congenital abnormalities including; (2) Meningocœle, spina bifida occulta. (3) Absent dome of the left diaphragm with herniation of stomach, double spleen, left adrenal and upper pole of kidney. The left lung is atelectatic and heart pushed over to the right. (4) Unrotated head of the pancreas, unicornuate uterus. (5) Absence of ribs 2, 3 and 4 on right side.

*Microscopic*: no significant changes in the organs.

*Conclusions*: Iniencephalus and other congenital anomalies.

Talipes, the most commonly associated abnormality was not present in either case. Absent diaphragm was found in one case. Neither case offered any serious complication to delivery. In both cases, the suspicion of congenital abnormality was aroused by polyhydramnios and confirmed by subsequent radiograph. Instances of this abnormality in males, as in the first case, are very rare, only 5 having been reported to date.

The total number of deliveries in this hospital during this 21 month period was 3,460, giving an incidence of 1 in 1,730 deliveries. This is considerably lower than Paterson's incidence of 1 in roughly 900 deliveries.

My thanks are due to Drs. E. F. E. Black and R. B. Mitchell for permission to use these cases, to Dr. A. E. Childe of the Department of Radiology and Dr. D. W. Penner of the Department of Pathology of the Winnipeg General Hospital for their reports.

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History is studded with critical dates—wars, invasions, revolutions, discoveries, peace treaties—that are firmly implanted in our minds. One of the least publicized of recent dates, yet one which is likely to have the greatest impact on the peace, security, and health of humanity at large, is July 22, 1946.

On that date sixty-one nations, probably the largest number of nations in the history of mankind ever to agree on the same principles, signed the Constitution of the World Health Organization. The decision to adopt the term "World" as part of the title of the new Organization served to emphasize the dominant concept that the peoples of the world cannot exist half sick and half well, any more than they can exist half slave and half free; those problems which are no longer purely national must be solved not only by international action, but on a world-wide basis.—Brock Chisholm.

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# EDITORIAL

## DICHOTOMY

DICHOTOMY is a botanical term meaning division into two parts, or it may be, repeated branching. As we use it however it has come to mean the division of fees for professional services where more than one doctor is concerned. It has also acquired an undesirable significance under certain circumstances and is clearly condemned by the principles of our medical ethics. In condemning it, however, we must understand exactly what is meant by division of fees. Obviously there can be no objection to the arrangement by which a composite fee is collected in group practice and is then divided amongst the members of the group. That is a well recognized plan of practice by which both sides benefit. Nor can there be any harm in rendering to a patient an account which shows the inclusion of a fee for an assistant, or anæsthetist. But when a patient is sent to a consultant who understands that he is to give a portion of the fee to the doctor referring the case a new and unsavoury element creeps in. To begin with there is deceit, for the patient does not know that his bill includes this commission. But, much worse, the tendency to exploit patients is born, and both the consultant and the man who sends him patients under this arrangement face intolerable temptation.

In the States another aspect of dichotomy has developed in connection with technical specialties such as roentgenology and optical agencies. This reached a stage at which the Department of Justice issued indictments against certain manufacturing agencies and several ophthalmologists. We are not to think that this may not come about in Canada if dichotomy is allowed to continue without protest.

The subject is a painful one, but should be faced as frankly as has been done by Dr. W. E. Gallie in his recent Lister Lecture.*

* September, 1948, this *Journal*.

# EDITORIAL COMMENTS

## The Prescription of Narcotics

A recent circular from the Department of Narcotic Control draws attention to the legal requirements in prescribing narcotics. These regulations have been repeatedly issued to members of the profession. In essence, no order for a narcotic can legally be filled by a druggist unless he has a signed prescription therefor. The only exception to this is in the case of codeine compounds containing an eighth of a grain of codeine per tablet or capsule, or not more than one-third of a grain per fluid ounce in proper combination with other ingredients.

The Department finds that these regulations are being disregarded by some physicians, who insist on telephoning their narcotic prescriptions to retail drug stores, and sometimes even demand that the medication be delivered to the patient before the druggist receives the prescription. The druggist who accedes to this request definitely violates the law as laid down in the Opium and Narcotic Drug Act.

The circular even quotes instances of druggists being told by physicians that if these telephone orders are not accepted the business will be diverted elsewhere. In such circumstances the physician becomes party to and is guilty of an offence under the Criminal Code.

We can only endorse the very soberly expressed desire of the Division of Narcotic Control that physicians should give their fullest co-operation in support of regulations admirably designed to maintain high standards of narcotic control.

## The X-ray in Tuberculosis

The development of x-ray examination of the chest in large groups of people has been spectacular. It has extended to all classes and many industries, and as an index of public health activity is impressive. But, as is wisely pointed out by Weber, Chief of the Tuberculosis Division of the United States Public Health Service (*U.S. Pub. Health Rep.*, **63**: 1027, 1948) all this effort is no more than a prelude to the more difficult matter of dealing with the disease after it has been detected. All the more important is this because most of the cases thus brought to light are in an early stage, and to that extent require the more careful management. It is not always easy to convince such patients that they have enough disease to justify months of observation and treatment. For with the most careful assessment of all the factors in the case it often is not possible to be sure of its degree of activity. And even with the most scrupulous care a lesion which may have been considered as completely arrested will for no apparent reason break down. Dr. Weber speaks of edu-

cating the community generally to accept the principle of careful and prolonged treatment in these earliest non-symptomatic stages. But we in Canada have an additional problem in providing this essential sanatorium care. We are a long way yet from possessing enough beds to care even for the advanced and well established cases, much less these very early ones. It is not much use discovering what cannot be remedied. It is at this stage of the struggle against tuberculosis that there should be full recognition by government agencies of the support they should give to the work.

## MEN and BOOKS

### SIR THOMAS BROWNE AND HIS CONTEMPORARIES*

**David J. Lewis, B.A.**

*Montreal, Que.*

If we were to think of the century in modern times which has been most neglected by the historians, the seventeenth would be first in mind. Certain of its great events, the Great Plague, the Thirty Years War and the English Civil War, might be remembered, but little else.

And yet in its way the seventeenth century was as interesting as any. It saw the passing of the golden Renaissance and the rise of the new sciences which have determined the nature of our times. In the setting splendour of the Elizabethan tradition there were men like John Donne, Milton and Sir Thomas Browne, who shared Shakespeare's extravagant magnificence of style. And on the other, brilliant minds like Isaac Newton, Harvey and Sydenham, who led the way in modern science. Descartes, Spinoza and John Locke laid the foundations of modern philosophy. It is not often that so many brilliant minds crowd on the stage together. The history of mankind had recorded nothing equal since the days of the ancient Greeks.

In our day, if a man sets himself to encompass the entire field of human knowledge, he must inevitably fail. But in those days it was different. It was still possible for a man to fulfil Matthew Arnold's definition of culture, to know everything worthwhile that the human race had thought or done. Such a one was Sir Thomas Browne.

He was born in 1605, the year of the Guy Fawkes gunpowder plot, which might have put a spectacular end to a dull king. In that year Shakespeare produced *Macbeth* and *King Lear*, and Queen Elizabeth was only two years dead. Browne's father was apparently well-to-do, but he died during the boy's early years. Thomas was very fortunate in his mother's choice of a second husband, Sir Thomas Dutton, who treated the boy as his own son, and had him educated at Winchester and Oxford. It is known that the youth visited the famous medical colleges of Montpellier, Padua and Leyden during the course of his grand tour on the continent. It was at the university of Leyden that he received his doctorate.

He was close on thirty years of age when he returned to England and wrote his most famous work, the *Religio Medici*. Being of a retiring disposition, the author did not rush to the press with it. The volume circulated amongst enthusiastic friends for several years, and then suddenly appeared in print. Browne expressed some horror at this "pirating" of his work, and at the garbled state in which it appeared. However he did not seem angry enough to change printers when the third corrected edition was put out. Historians tell us that it was a common ruse for fledgling authors of those days to have a "pirated" edition of their first work. If the book succeeded they could proudly step up and claim their due. If it dropped deadborn from the press, their literary virginity was still secure. Dr. Johnson, who wrote a rather disdainful life of Browne some three-quarters of a century after he was safely under ground, imputed this piracy stratagem to him; but there does not seem to be much evidence either way.

In 1637, some of Browne's friends prevailed on him to come and set up practice in Norwich. Browne was associated with this East Anglian town for the rest of his long life.

#### BROWNE AND THE CIVIL WAR

Meanwhile in the public life of England a crisis had developed. The country was divided against itself. At the end of a five-year civil war, King Charles I was sold across the counter for Scotch army pay arrears. Cromwell decided to kill the king, and purged the House of Commons down to fifty "reliable" members. These were a pack of religious fanatics. They were so divorced from true piety that they called themselves such blasphemous names as "Praise-God Barebones", "Christ - Came - Into - The - World - To - Save Barebones", and even "If - Christ - Had - Not - Come - Into - The - World - Thou - Hadst - Been - Damn'd Barebones". With a jury such as this, there was little trouble in finding the king guilty of treason and having him sentenced to death by beheading.

The execution of the king was followed by Parliamentary Government, and then the five-year military dictatorship of Cromwell. After the miserable showing of the dictator's son,

* Read before the Osler Society, McGill University, November, 1947.

Richard, King Charles II was restored to his father's throne.

This political struggle seems to have left little impression on the serene doctor. He was a confirmed loyalist, but he did not show any desire to quit his part of the country, which was strongly Roundhead. Except for calling the King's execution a "horrid Murther" and refusing to subscribe money to the Puritan forces, he seems to have cultivated his garden in tranquillity.

Browne's contemporary, the famous William Harvey, was much less fortunate. With his experiments on the circulation of the blood long behind him, Harvey was 64 at that time. This age meant much more to a man in those days than it does now, but he still attended the king in the field. There is a legendary story told of Harvey at the Battle of Edgehill, to the effect that the old physician was given charge of the king's two sons, the Prince of Wales and the Duke of York. Harvey does not seem to have been terribly interested in the progress of the battle, because he retired forthwith to the shelter of the first hedge, taking his charges with him. Here he pulled out a book and immediately became engrossed in it. Just at that moment a cannonball whizzed past his ear. The old physician arose with dignified annoyance and retired to the next hedge, where he once more fell to reading.

Harvey lost a great many manuscripts when his house in London was pillaged by a mob. Several of these were unpublished scientific works, which he felt himself too old to write over again.

But to return to Thomas Browne. In the *Religio Medici* he had expressed some distaste for the brute facts of matrimony:

> "I could be content that we might procreate like trees without conjunction, or that there were a way to perpetuate the world without this trivial and vulgar way of union. It is the foolishest thing a wise man ever commits in all his life; nor is there anything which will more deject his cool'd imagination when he shall consider what an odd and unworthy piece of folly he hath committed. I speak not from prejudice, nor am averse from that sweet sex, but naturally amorous of all that is beautiful."

There is something in the English public school system which seems to militate against the development of sex maturity in its products. How often one meets young English boys of this class who have arrived at precocious intellectual maturity at fourteen; but who still think of women as strange, mysterious, dangerous creatures when they themselves have arrived at their thirties. It appears that this phenomenon is at least three hundred years old, because Browne gives every evidence of having been such a one.

Although Browne faced considerable ridicule by getting married, he chose well. A neighbouring person has said of his choice, Dorothy Mileham, that she was "a lady of such symmetrical proportion to her worthy husband, that they seemed to be drawn together by a sort of natural magnetism". The match seems to have been well worth the chaffing involved, and the author overcame his qualms to the extent of fathering ten children. Of these, a son, Edward, was to become a well-known London physician, fellow of the Royal Society, and traveller. Another son was doing well in the navy when his career was unfortunately cut short. His letters to his father are full of interesting sidelights on the Royal Navy, which was at that time at its lowest ebb, neglected by politicians, unpaid and mutinous.

### BROWNE KNIGHTED BY CHARLES II

Towards the end of his life Browne was knighted by the king. Charles II, in 1671, was carousing with his profligate court at Newmarket, long a royal playground. Making an excursion to Norwich he was entertained for a week by the mayor and corporation at enormous expense. Wishing to knight someone before he left, the Merry Monarch called for the mayor. But curiously enough this worthy was unwilling, and the honour was thrust upon Browne. However, even if the honour did come in through the back door, it was well merited. Dr. Johnson remarked that it was a good trait in this profligate monarch that he had the discernment to reward merit, especially when it cost him nothing.

Browne's life ended on his birthday in 1683. This curious coincidence is given considerable point, because we know that this thought had been in his mind before. In "A Letter to a Friend" he had written of the strange harmony in some lives "that the first day should make the last, that the tail of the serpent should return into its mouth precisely at that time and that they should wind up on the day of their nativity".

Mr. Thomas Whitefoot, the good parson whom we have already heard describing Mrs. Browne, has left us an interesting description of the author's appearance:

> "His complexion was answerable to his name (Browne, I suppose) and (his) Habit of Body (was) neither fat nor lean, but well fleshed. . . . He was never seen to be transported with mirth, nor dejected with sadness; always cheerful, but rarely merry . . . his gravity was natural without affectation."

It is a curious thing about him that he seems always to have been close to blushing. Every time he made a joke, he accompanied it with a blush. His friends noted that he often blushed without any obvious reason, apparently at some joke he was having with himself. In spite of all this, the author considered himself "as wholesome a morsel for the worms as any".

## LITERARY WORKS

Browne wrote six major works which are still read today. The most famous, the *Religio Medici,* was written when he was at the cross roads between his medical studies and his practice. It would seem to be the result of that soul-searching which Descartes and Osler recommend to a man once in his life and once only. In this interesting piece of philosophizing, he tells his beliefs and opinions in matchless language. His broad, mellow religion enabled him to see the good in every faith from that of the Roman Catholic to the meeting-houses of the Dissenters. In a ferociously controversial century, his broadmindedness is a very welcome breath of fresh air.

The religious aspirations of the average medical man might be summed up in a little epitaph written by George Macdonald:

> Here lie I, Martin Elginbrodde;
> Hae mercy o' my soul, Lord God;
> As I would do were I Lord God,
> And ye were Martin Elginbrodde.

The average medical man feels he has done pretty well for his neighbour during his busy life, and more or less expects the Good Lord to keep him out of hot corners in the next world. Browne's attitude is rather different. He feels that he cannot do enough for his God. There is no doubt that he made Him a sacrifice of his independence of mind. Most people are content to give the Lord what they are constitutionally incapable of using anyway. Perhaps it was this way with Browne. At any rate he passed to the end of his life with an implicit belief in witchcraft, because it was recommended in Holy Writ. He refused to consider Galileo's theory of astronomy because it did not jib with Genesis. However, he did derive some spiritual justification for his scientific inquiries from religion. He wrote:

> "The wisdom of God receives small honour from those vulgar heads that stare about, and with a gross simplicity admire his works. Those highly magnify him whose judicious inquiry into his acts and deliberate research into his creatures, return the duty of a devout and learned admiration."

In other words, science is a dignified compliment to God.

The *Religio* achieved an immediate popularity not only in England, but later on the continent. It had the good fortune to provoke not a short article as a review, but a whole book. The reviewer, Sir Kenelm Digby, was a courtier and man about science of those days. Of his volume Dr. Johnson said that its chief merit was that it was written within the space of twenty-four hours, including the time taken to send out for the *Religio* and read it. The *Religio* was translated into many languages. Possibly because of dogmatical differences or because they were allergic to his broad-mindedness, numerous critics hurled themselves like wild dogs upon the book. One of them, Tobias Wagner, said that "the seeds of atheistic impiety are so scattered throughout the book that it can hardly be read without danger of infection".

During the eighteenth century the volume lost favour to a considerable degree. The style of the volume could hardly be crammed into the rigid canons of simplicity of those days. However, it will be remembered that some of Shakespeare's plays had to be rewritten to suite the delicate taste of the Augustan era. However with the Romantic Revival the book was hailed by Charles Lamb, and the popularity to which he restored it has never since waned. Doctors by the hundreds have found it to be the kind of book one keeps by one's bedside for years at a time, deriving from it inspiration and comfort. None of you will have to be reminded that Osler felt that no other volume had had so much influence in his life. A Montreal doctor was engaged in a *Religio Chirurgi* when death overtook him earlier this year (1947). There have been many other books written in imitation of it.

Browne's largest book is the *Pseudodoxia Epidemica,* or *Enquiries into Very Many Received Tenents and Commonly Presumed Truths.* The book is Browne's attempt to clear away the mass of errors which cluttered up science and literature in those days. As a source for antique stories and anecdotes it has great value. As in most of Browne's works, there is more to it than just the subject matter. He has a gift for the picturesque, and an interesting way of writing which comes from having studied human nature as well as books.

*Urn Burial* was theoretically a monograph on certain funeral urns found near Norwich, but it ended up as a superb oration on the death customs of men throughout history. Death had a peculiar fascination for the men of those days. It was felt that if a man had one foot in this world and another in the next, he must have the wisdom of both existences. Old men were as meticulous as actors in rehearsing their deathbed scenes. People flocked to watch public executions of criminals, and their scaffold harangues were printed and eagerly read by an admiring public. Browne unleashed the whole splendour of his orotund style on this macabre subject, and gave the world one of its most sustained and elevated pieces of writing.

He wrote other works of which little need be said here. They include *A Letter to a Friend, The Garden of Cyrus,* and *Christian Morals.* The tone of the latter reminds one very much of Lord Chesterfield's *Letters to His Son,* but the moral tone is somewhat higher.

As a physician, Browne seems to have been excellent for those days. He naturally possessed from his earliest years that equanimity of which Osler made so much. In addition to this he had a true feeling for his patients.

"Let me be sick myself if sometimes the malady of my patient be not a disease unto me. I desire to cure his infirmities rather than my own necessities. . . . I am not only ashamed, but heartily sorry that besides death there are diseases incurable; not for my sake, or that they are beyond mine art, but for the general cause and sake of humanity, whose common cause I apprehend mine own."

No cynic could say that this man's equanimity was only the ability to observe the misfortunes of others with contentment.

### BROWNE'S PLACE IN SCIENCE

In science Browne has been acclaimed by some as a pioneer in chemical embryology. This field was then being touched on by Harvey. There is no doubt that Browne did do some experiments too. For instance he put some vinegar in an egg, thus observing the effect of increased hydrogen ion concentration on the early vital processes of an avian embryo. No one will quarrel with this. A quick look through his notebook might also convince one that he was a pioneer in protein and colloidal chemistry, physiology, physics, zoology, botany, archæology and so on. Browne carried out a great many diverse and diverting experiments in his 77 years. But if we are to leave any meaning in the term "scientific pioneer," we cannot use it for him.

It might be well at this point to ask ourselves the question, "Just what kind of a person could have caused a great advance in science in those days?" First of all, it would have been almost impossible for a man to have caused great advances in many fields at one time. The pioneer would have to be a specialist. Secondly, before a man can make useful theories, he must have a detailed knowledge of his field. The pioneer would have to be an eminently practical man. His ideas must needs be sweeping in their application, but clear and simple in conception.

Thomas Sydenham was a good example of this type. He was born twenty years after Browne, and did not gravitate into medicine until after he had fought as a captain of horse in the Roundhead army. All through his life he remained a practical man, relying on his own acute observation of disease processes rather than the high-flown theories of his contemporaries in medicine. He told several people that *Don Quixote* was as good a textbook of medicine as any, leaving it to his hearers to decide whether the Spanish novel was good or the textbooks poor. It is particularly noticeable about this eminently practical man that he rarely stepped outside his own field. When he did he was undistinguished. It was he who gave us much of our modern classification of disease, and described gout, measles, dysentery, chorea, hysteria, and several other conditions.

To my mind Browne was temperamentally unsuited to scientific research. He was primarily the artist type. With an artist's contempt for hard facts, he intended to ignore a planned program of research. He does not seemed to have tried very hard to rule out variables. If there is any quality a successful scientist must have in abundance it is persistence. Browne was too easily turned aside. Any block in his experiments produced a splendid show of mental fireworks. After this he sought a new field of effort. Harvey spent ten years of his life establishing his theory of the circulation of the blood. But one could never imagine Browne doing anything like that.

In surgery a considerable advance had taken place after Vesalius had reformed the teaching of anatomy. Surgeons of Ambroise Paré's time operated with a knowledge of human anatomy, and not of Galen's dogs and swine and monkeys. But medicine was still enshrouded in the nubeculæ of the dark ages. When Sydenham's books began to dispel the mists, Browne was 63 and not liable to change his whole habit of thought just because a new medical book had appeared on the market.

In Browne we see great learning, but no great attempt to distinguish between truth and tradition. We know it was not laziness, for he never spared himself. Practically all of his spare time was spent in study and in correspondence with the foremost men in science of his day. But one cannot help wondering whether he did not often value science for the opportunities it gave him for colourful writings and apt quotation. Very often we seem to see the instinct for research running a bad second to the author's fantasies.

He is not without a certain strain of gullibility. It gives one food for thought to know that there are several pages in the *Pseudodoxia Epidemica* devoted to the question of whether badgers have shorter legs on one side than on the other (tradition "ascribed the brevity unto the left"). Surely in a series of ten badgers this interesting enigma could have been solved at the expense of less printer's ink and without the necessity of quoting Albertus Magnus and Aldrovandus. The error has lately reared its ugly head in our own country in the form of the roundhill gouger of New Brunswick and the Rocky Mountains. So it does not appear that the colourful literary badgerhunt which Browne started was eminently successful.

Elsewhere in the volume he describes his approach to another problem: "A kingfisher hanged by the bill sheweth in what quarter the wind is by an occult and secret property, converting the breast to that point of the horizon from which the wind doth blow". Browne put this to the test under rigorous experimental conditions, and indoors. Here are the results:

"If a single Kingfisher be hanged up with untwisted silk in an open room, where the air is free, it observes not a constant respect unto the mouth of the wind, but variously converting, doth seldom breast it right. If two be suspended in the same room, they will not regularly conform their breasts, but ofttimes respect the opposite points of heaven."

As a corollary to this experiment, Browne condemns the tradition of hanging up dead birds in the belief that they will renew their feathers every year just as in life. The opinion of Albertus Magnus was to the contrary, our author noted. In the same book Browne proves, with the aid of Holy Scripture and many secular authors, that it is untrue "That Storks will live only in Republickes and Free States".

Sometimes it is hard to discover at this distance whether Browne was playing the fool or actually being one. The game of building things up and knocking them down is still being played in our time. Unfortunately few of the present day debunkers have displayed either the learning or talents of Sir Thomas. If Browne had lived at any time later than he did, his light would have been dimmer. He was the last of those Renaissance men who bestrode their narrow intellectual world. Although he was not the greatest of them, he is one of the few who left anything which edifies the reader today. None of us is interested in his facts so much as in his ability to follow an idea from the heights of heaven to the depths of hell and back by way of Cathay and the gold mines of Potosi in the New World. He managed to keep up the wealth of metaphor and allusion so characteristic of the Elizabethans. And there is the same beautiful roll in his sentences. Dr. Johnson taxed Browne with overstraining the English language, but even he was forced to admit that "his heights could never have been reached but by one who had little fear of falling".

Browne's books are not to be gulped down in massive draughts. They enjoy him most who roll his words and ideas round their brains like an old gourmet savouring a fine liqueur.

## Canadian Physicians' Fine Art and Camera Salon


"Open Water in March". By Dr. G. E. Tremble, Montreal. Accorded first prize in the Fine Art Section (Sponsored by Messrs. Frank Horner, Ltd., Montreal).

There is little doubt that his kind of mind must hold itself in strongly if it is to get very far in scientific investigation. Francis Bacon was close to the heart of Browne's psychological problem and to the problem of all scientists when he wrote:

> "Generally let every student of nature take this as a rule—that whatever his mind seizes and dwells upon with peculiar satisfaction is to be held in suspicion, and that so much the more care is to be taken in dealing with such questions, to keep the understanding even and clear."

Again it is possible for a man's mind to become so engorged with ideas that it becomes immobile, like those ants that turn themselves into living honey jars, hanging for the remainder of their lives from the roof of a formicary storeroom. The very quantity of ideas that Browne engulfed and kept at the ready may have stunted his efforts at research. "He that observeth the wind shall not sow, and he that regardeth the clouds shall not reap." In science as well as in literature, Browne sowed heavily, but his harvest was only his books.

And perhaps it was well that it was so. Many thousands have sought immortality in science, and some few have attained it. They have their names emblazoned on statuary and the walls of scientific edifices. Others have lived on a few years in the literature. But it is all at best a kind of tombstone immortality. A different fate awaited Browne. His gentle ghost, shrouded in this thin volume, can come to any of us in the quiet of our evenings. Who could desire a better way to be remembered?

# MEDICAL SOCIETIES

## Montreal Medico-Chirurgical Society

The November meetings of this Society will be as follows: November 5, Dr. Frank L. Horsfall, Jr., The Hospital of the Rockefeller Institute for Medical Research, New York City, "Prospects for the Control of Viral Diseases with Chemical Agents". November 19, a clinical meeting will be held at the Queen Mary Veterans' Hospital, Montreal.

## New Brunswick Medical Society Annual Meeting

The sixty-eighth annual meeting of the N.B. Medical Society, a Division of the C.M.A. was held at Bathurst, N.B., September 6, 7, and 8. The scientific papers were exceptionally good and a large registration of physicians fully enjoyed this portion of the program.

The speakers and their subjects were: (1) Dr. Adrian Anglin, Toronto, "The Management of Bronchial Asthma". (2) Dr. Wm. Magner, Toronto, "The Interpretation of Jaundice'. (3) Dr. W. J. McNally, Montreal, "Some Remarks About Dizziness". (4) Dr. Gordon Morrison, Boston, (*a*) "Fractures of the Ankle Joint", (*b*) "Fractures of the Neck of the Femur". (5) Dr. S. J. Martin, Montreal, "Carcinoma of the Breast". Dr. Arthur Melanson, Fredericton, "Some thoughts on Public Health in New Brunswick".

In addition Round Table Conferences were held as follows: (1) medicine, anæmia—Chairman, Dr. N. Skinner; (2) surgery, fracture, femoral neck—Chairman, Dr. Alex. McLennan; (3) obstetrics, "Posterior Positions"—Chairman, Dr. Geo. White.

The commercial exhibits were this year of increasing interest. Entertainment at Bathurst is always in a class beyond compare and from the President's reception on Monday evening, through the annual dance and President's Garden Party all enjoyed meeting old and making new friends. The garden party on the President's lawn was blessed by beautiful weather, allowing full appreciations of the lovely garden, facing the river. At the luncheon on Wednesday, the retiring President gave a short review of the year's work, but spent most of his time in pointing to progress already mapped for the future and indicated the evident duties to fall on the oncomers in medicine in our province. At this same luncheon Dr. Wm. Magner, C.M.A. president, humorously and sincerely gave his views on the present trends in the practice of medicine. Dr. Kelly brought the society up to date on policy of the C.M.A. and throughout the meeting was generous with advice and in providing expedients in procedure.

Among the various annual reports presented, a few were outstanding. The Workmen's Compensation Buffer Committee, reported amicable negotiations with the board, which resulted in an agreed increase in fees for office treatments and a satisfactory fee arrangement for treatment of several conditions, over which there has been long standing controversy. This report was read by Dr. Geo. F. Skinner, chairman of the committee.

The cancer committee chairman, Dr. John R. Nugent, gave a full and interesting résumé of a year's hard work by active working committees and indicated that most likely in 1948-49, further facilities would be made available in the province by increasing co-operation between members of the Society and the Provincial Department of Health. It was recommended unanimously that treatment of cancer in any provincial scheme be directed only by fully qualified and certified physicians.

Discussions of prepaid surgical and medical care were careful and thoughtful and it was again referred to a special committee for further study.

Dr. C. L. Gass presented a splendid report from the Hospital Planning Committee, on which he represents the Society.

The 69th Annual Meeting of the Society will be held in Fredericton.

The election of officers provided the following for the year 1948-49: *President*—Dr. G. E. Chalmers; *First Vice President*—Dr. W. W. Fleck; *Second Vice President*—Dr. E. O. Thomas; *Treasurer*—Dr. A. L. Donovan; *Secretary*—Dr. R. A. H. MacKeen.

## Meetings of Societies

1. On September 9, 10 and 11, District No. 10 of the Ontario Medical Association held a District Medical Meeting at Fort William and Port Arthur. Clinics were given by Drs. D. L. C. Bingham and E. M. Robertson of Kingston and by Dr. F. S. Brien of London, Ont. Dr. Bingham also spoke on "Essential Hypertension and its Surgical Treatment"; Dr. Brien on "A Clinical Approach to the Anæmic Patient", Medical Aspects of Peripheral Vascular Disease" and Dr. Robertson on "Some Aspects of the Law in Relation to Problems in Gynæcological Obstetrics". At an evening session, Dr. Robertson gave an address on "Twins, Chicago, the Bible, Shakespeare, Verse". Dr. W. V. Johnston, President-Elect of the Ontario Medical Association also addressed the meeting. An Annual Dinner was held at the Fort William Country Club.

2. The District Medical Meeting of District No. 7 of the Ontario Medical Association was held on September 15 in Gananoque at the Blinkbonnie Hotel. After a business meeting, papers were read by Dr. Melville C. Watson, of Toronto on "The Toxæmias of Pregnancy" and "Physicians' Services Incorporated" and by Dr.

W. A. Oille of Toronto on "Hypertension and Arteriosclerosis". At the evening dinner, the speaker was Dr. W. V. Johnston, President-Elect of the Ontario Medical Association.

3. At the 8th Medical Alumni Lectureship of the University of Western Ontario, on October 12 and 13, the guest lecturer was Prof. John McMichael, Professor of Medicine, British Postgraduate School of Medicine, University of London. Former R.C.A.M.C. officers will recall his Wednesday Ward Rounds at Hammersmith.

4. On September 22, the District Medical Meeting of District No. 3 of the Ontario Medical Association was held in Walkerton, Ont. The program consisted of a business meeting and papers by Dr. L. S. Barnes, of Toronto on "Diseases of the Eye, Ear, Nose and Throat from the Standpoint of the General Practitioner" and Dr. Irwin Hilliard of Toronto on "Bronchitis, Bronchiectasis and Bronchial Asthma". Dr. W. V. Johnston, President-Elect of the Ontario Medical Association addressed the meeting. The evening session was held at Pleasure Valley Farm. The guest speaker was Dr. L. Joslyn Rogers of Toronto and his subject was "Medicine and Crime Detection". After bridge and golf at the Walkerton Golf and Country Club, the ladies joined the doctors at the dinner.

5. District No. 1 of the Ontario Medical Association held their District Medical Meeting at the Public General Hospital, Chatham, on September 28 and 29. A business meeting was held the first day. Next day clinics were given by local members of the Kent Medical Society followed by papers on "Observation on the Nature and Consequences of those Injuries to which the Head is Liable from External Violence" by Dr. Frederick Schreiber, of Wayne University College, Detroit; "The Neuroses in General Practice" by Dr. Foster Kennedy, Cornell University, New York, and "The Anæmias" by Dr. Ray Farquharson, University of Toronto. A dinner was held at the William Pitt Hotel, Chatham and the guest speakers were Dr. W. V. Johnston, President-Elect of the Ontario Medical Association and Dr. Foster Kennedy. The latter spoke on "The Rôle of the Physician—Psychiatrist in Public Affairs".

## Defence Medical Association of Canada
## Central Ontario Branch

On September 27, 1948, with Colonel Milton Brown, the president as chairman, the annual meeting of the Central Ontario Branch of the Defence Medical Association was held. A number of resolutions were discussed and prepared for submission to the annual meeting to be held at Ottawa on November 5 and 6, 1948. The executive for the ensuing year was elected, consisting of the following: *President*—Col. H. T. Ewart; *Vice-Presidents* — Lieut.-Col. Magnus Spence, Surg. Lieut.-Cmdr. J. M. Parker; *Secretary-Treasurer*—Lieut.-Col. A. E. Parks.

This association is an important one, authorized by the Government of Canada. All ex-service medical officers resident in the Central Ontario area are cordially invited to become members of this branch, and it would be appreciated if their names and addresses, together with the annual fee of $2.00, could be forwarded to the Secretary-Treasurer, Lieut.-Col. A. E. Parks, 330 University Ave., Toronto 1.

District Number Eight comprising the counties of Carleton, Russell, Prescott, Glengarry, Stormont, Dundas, Renfrew and Lanark held their meeting at Renfrew on October 6. Visiting speakers were: Dr. D. L. C. Bingham, Kingston; Dr. J. E. Plunkett and Dr. J. C. Whyte of Ottawa. Dr. L. Wallace of Renfrew gave a talk on "Experiences with Eskimos of Aklavik".

District Number Four comprising the counties of Haldimand, Lincoln, Welland, Wentworth and Halton held their meeting at Hamilton October 12 and 13. Clinics and lectures were given by members of the staffs of Hamilton General and St. Joseph's Hospitals.

District Number Six comprising the counties of Victoria, Haliburton, Peterborough, Durham, Northumberland, Prince Edward and Hastings held their meeting at Peterborough October 19 and 20. Visiting speakers were: Dr. C. E. Snelling, Dr. R. B. Kerr and Dr. R. C. Laird all of Toronto.

Dr. W. V. Johnson, Lucknow, President-Elect of the Ontario Medical Association spoke at each of these meetings.

# CANADIAN ARMED FORCES

## News of the Medical Services

His Majesty's Canadian Ships *Ontario, Antigonish, Crescent* and *Athabaskan* depart for Pearl Harbour on a training cruise October 11, returning to Esquimalt, B.C., November 10, 1948. Surg. Lieut.-Cmdr. C. M. Harlow, Halifax, N.S., Surg. Lieut.-Cmdr. W. D. Love, Vancouver, B.C., Surg. Lieut. W. S. Patterson, Kingston, Ont., and Surg. Lieut. J. A. Boyd of Saskatoon, Sask., all members of the Royal Canadian Navy (Reserve) will participate in this interesting cruise.

Surgeon Captain A. McCallum, O.B.E., Medical Director General of the Royal Canadian Navy, was the official delegate of the Canadian Armed Forces Medical Services attending the International Committee on Military Medicine and Pharmacy, Stockholm, August 18 to 20, 1948, the International Red Cross Conference, Stockholm, August 20 to 30, 1948, and the Hungarian Medical Week, Budapest, September 4 to 12, 1948.

At the request of the Secretary of State for External Affairs, Lieut.-Col. J. N. Crawford, M.B.E., E.D., R.C.A.M.C., of the D.G.M.S. Directorate, attended the Seventeenth International Red Cross Conference in Stockholm, as a member of the Canadian Government Delegation to the Diplomatic Conference for the proposed revision of the Geneva Convention. While the subject should be of considerable interest to the profession in this country, an account of the proceedings would require much more space than can be given here; it is hoped that a complete report can be published in the *Journal* at a later date.

The work of the conference demanded full time attendance during weekdays, but the delegates found time on the two Sundays during the period to see something of Stockholm and its environs. Two tours were arranged, one to Saltsjobaden, a nearby summer resort, and the other to Uppsala, the university town of Sweden. Most of the free evenings were given over to official receptions, including one given by the heir apparent to the Swedish Crown and his Princess. The Canadian delegation travelled by air via London and Copenhagen both going and returning, and the entire trip was completed in just under three weeks.

The Canadian Officers Training Corps program for 1948 included the employment during the summer of second and third year medical students as clinical clerks in military hospitals and D.V.A. hospitals to which military medical staffs are attached. Fifty-four in number, and cadets had all received basic military training during previous years at the R.C.A.M.C. School in Camp Borden, and represented every medical school in the Dominion. The summer's work, though largely clinical in nature, included a study course given by the R.C.A.M.C. Hospital staffs, designed to complete their military qualification. The students assigned to the

larger D.V.A. hospitals had the advantage of more elaborate training facilities, but those attached to the outpost hospitals gained much practical experience.

As part of the larger C.O.T.C. plan for the production of a nucleus of trained officers available for an emergency, the medical plan has gone beyond the Army requirement, and should help the student in his more senior academic studies.

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Arrangements have been completed for a representative of each of the Medical Services of the Canadian Armed Forces to attend the annual convention of the Association of Military Surgeons of the United States. This convention is to be held in Fort Sam Houston, San Antonio, Texas, on November 10, 11, 12 and 13, 1948.

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Nursing Sister V. Bransagger was posted to the three months' Flight Nurses Course at Air University, School of Aviation Medicine, Randolph Field, Texas. The requirement of Nursing Sisters fully qualified in all phases of transportation of patients by air continues in peacetime and the R.C.A.F. will maintain a nucleus of such personnel.

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During the past summer, over fifty under-graduates representing all medical schools, were employed at selected sites by the R.C.A.F. Medical Branch. Under existing policy, these undergraduates were selected from ex-aircrew of World War II, all of whom had had operational experience. This background made their work mutually beneficial, as they were employed on development projects on the medical aspects of flight and this program was supervised by the Institute of Aviation Medicine. These ex-aircrew men, with their many personal experiences, have shown a very realistic approach in their work in aviation medicine.

# CORRESPONDENCE

## Diagnosis of Carcinoma

*To the Editor:*

In Prof. Robertson's analysis of results with the smear technique for the diagnosis of carcinoma in your issue of August 1948 there are a number of points to which I desire to draw attention.

1. *Incidence of malignancy.*—In smears from the vagina and cervix a population sample of less than 1,262 is dealt with since this figure includes first and repeat specimens. In this sampling, allowing for incorrect positives and negatives, 40 cases of undoubted carcinoma and 33 "suspicious, probably benign" lesions are claimed to be discovered. Unless repeated specimens were taken from positive cases one is driven to the conclusion that in this population sample there is an incidence of undoubted malignancy of cervix and endometrium of more than 3%. The Regina Cancer Clinic dealt with 40 new cases of carcinoma of the cervix or body of the uterus in 1947. The population covered by the Clinic is between four and five hundred thousand (the number of females in the cancer age is not immediately available). One might therefore assume that a sampling similar to Prof. Robertson's would disclose all, or almost all, our cancer cases. This would be an amazing result when one considers that the survey only entails the examination of 1,262 smears. Since no detail is given of the population sample one cannot analyze the results and compare them with other surveys but the figures are, to put it mildly, both alarming and amazing. It would be of interest to get a more detailed explanation.

2. *Criteria of malignancy.*—The incidence recorded being high one would naturally like to know more of the criteria used in the biopsy verification. In the cervix one is dealing with a particularly difficult problem. Few cervices in the cancer age are normal. Most show some sign of chronic inflammation. Epidermidization of mucous glands is common. In many the new epidermal layer is thickened and the basal layer is broken up by an infiltration of chronic inflammatory cells. Accordingly the question of early carcinoma is one of great difficulty. I am sure that most pathologists will agree with me that in many difficult cases the honest report will read somewhat as follows: "No absolute criteria of malignancy are present but it is equally impossible to definitely exclude early malignancy. Accordingly it would be wise to treat the condition as an example of early malignancy or to keep the case under observation". During the war years people in the United Kingdom were too preoccupied to go to their doctor except in the case of serious illness and medical services were greatly reduced. Nevertheless no post-war tide was experienced through this type of case coming to full fruition. Accordingly, on this score I am confident that pathologists err far on the safe side.

In view of the difficulties in diagnosis of suspicious cases I consider that in early work on the subject of smear diagnosis it would be advisable to have sections checked independently by a panel of pathologists, since, obviously, a limit must be put on how much one is allowed to err.

3. *Evaluation of the smear-test.*—Histopathology is a limited science; the examination of single cells for malignancy is even more limited. The main virtue of the smear technique must rest with the claim that it covers a sampling of the entire cervix, as opposed to biopsy which covers one small suspicious area. But the former claim must depend on a very exhaustive search covering a wide field because the ultimate diagnosis, except in flagrant cases, in the end rests on a tissue diagnosis in that the examiner reaches his conclusion by comparing and contrasting many cells. (This point should perhaps be more emphasized because reputable cytologists have not as yet claimed any method of recognizing a single cell taken out of its environment as being malignant.) The value of the method would, therefore, have to be assessed against the time taken to reveal the lesion by careful examination and biopsy. Prof. Robertson does not deal with this point specifically but (*a*) mentions that in one case a positive smear did not lead to verification until a small lesion was revealed after hysterectomy; (*b*) in 36 others no mention is made of difficulty in verifying a positive diagnosis; and (*c*) it is also admitted that the smear method missed five positive cases. It is to be hoped that any future investigation will be more searching in regard to these points. In addition, taken at face value, one would be entitled to say that those figures indicate that the new method is inferior to careful examination and biopsy since the new method disclosed one case undiscovered by the old method, while the old method disclosed five cases undiscovered by the new method.

4. *The question of "pre-cancer".*—Prof. Robertson mentions Meigs on the possibility of the smear method being able to reveal a malignant lesion a few cells in size, and some authors on the subject use the terms pre-cancer and early cancer with a deplorable looseness. In considering these questions in relation to smear diagnosis some consideration should be given to the work on experimental carcinogenesis pioneered by Peyton Rous. (*a*) It has been repeatedly shown that the application of a chemical carcinogen in sub-threshold doses to a tissue may lead to no visible change yet nevertheless the application of the carcinogen has led to a condition of "latent malignancy". The "latent malignancy" can be unmasked by applying at a later date a non-specific irritant to the tissue not in itself capable of producing cancer—trauma, chloroform, croton oil. (*b*) If threshold doses of carcinogens are applied to tissues, tumours develop after a latent period and this is preceded by a non-specific chronic inflammatory disturbance which is variable and has no constant or special criteria recognizable by present-day methods. (*c*) For every tumour

which comes to fruition after chemical induction many potential neoplastic foci regress.

Thus experimental work indicates that there can reside in a tissue an invisible cancer trait awaiting only a non-specific chronic inflammatory disturbance to bring forth the neoplastic potentiality. This potentiality may be brought forth multifocally but for every growth which succeeds in acquiring its own blood supply and emerging as an entity diagnosable as tumour by present methods there are a host which succumb. One must therefore approach the problem of pre-cancer, or early cancer, and of its relation to chronic inflammation, with humility and realize that when we do define them accurately and have tests to expose them we may find that it may be the rule to have many such lesions at some time in every human life.

5. *Popular appeal.*—While one cannot fail to be impressed by the monographs of Papanicolaou and Traut, and of Gates and Warren as scientific exercises one must also consider many other aspects of practical application. Prof. Robertson mentions that the smear test "must therefore appeal to many women". I respectfully submit that in this lies the real danger because I consider that at present the test has not been properly evaluated and much painstaking work lies ahead before general application can be undertaken. General discussion of the problem would be of value.

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Regina, Sask.

# SPECIAL CORRESPONDENCE

## The London Letter

*(From our own correspondent)*

### HEALTH CENTRES

The fact that up to date 92 to 93% of the population have registered under the national health service may well have been sufficient justification for the Minister of Health informing the Society of Medical Officers of Health at their recent annual dinner that he was "delighted" with the success of the service, but it must be confessed that he still has an unfortunate habit of stirring up unnecessary opposition. A glaring example of this is his Department's attitude over health centres. Whatever other criticisms there may have been of the new service, there has been practically nothing but praise for the idea of the health centres which were promised. In these, general practitioners, working in teams, would be able to attend to their patients in buildings specially built for the purpose and equipped with all the ancillary services necessary for the successful carrying out of general practice, including clerical assistance. Yet in January a ministerial circular was issued deprecating even experimental buildings for this purpose. Then in August the doctors of Birmingham were informed officially that they would not be allowed to see private patients in health centres set up under the national health service. As it is perfectly legitimate for a doctor to have private patients, this means that any doctor with private patients will be compelled to maintain, at considerable additional expense to himself, private consulting rooms in his own house. The other curious anomaly is that this decision penalizes the general practitioner, compared with his consultant colleagues who are allowed to carry on private practice in state-provided hospitals.

The one bright feature in this welter of ministerial obscurantism is that the Council of the British Medical Association has just published an interim report on health centres. This contains a comprehensive survey of the whole subject and detailed recommendations for the building and organizing of such centres. Once again the Minister is indebted to the profession for an outstanding contribution towards the vexed problem of how the new Service is to be made a success.

### INTERNATIONAL CONGRESS ON INDUSTRIAL MEDICINE

The Ninth International Congress on Industrial Medicine, which was held here early in September, has fully justified the optimism of its organizers. The first to be held in Great Britain, it was attended by about 750 delegates, of whom 270 came from abroad. The only possible criticism was of the lack of discrimination in the selection of papers. To expect adequate discussion of practically 200 papers is asking just a little too much of human nature. Perhaps the outstanding feature of the Congress to those who have followed the development of industrial medicine during the last fifty years was the amount of time and attention devoted to the psychological aspects of modern industry. Industrial hazards had their fair share of attention, but even here the increasing complexity of industrial processes introduced a note of specialization which would have been utterly foreign to the pioneers of this important branch of medicine.

### THE POST OFFICE MEDICAL SERVICE

One does not usually associate pioneering with government departments. The British Post Office, however, can claim to be such in the sphere of industrial medicine. Its medical service was inaugurated in 1854 and it first appointed a woman doctor in 1883. The institution of the national health service in July meant the end of the service as a separate entity, and this sad event has been made the occasion for a review of the service by the chief medical officer to the Post Office. Unfortunately, the records of the service prior to 1891 have been lost, but those that cover the remaining half century provide a wealth of valuable information. The figures are by no means comforting, and it is to be hoped that the full review will be carefully studied by all concerned. For instance, the total amount of sickness absence in the lower grades of the Post Office was higher in 1946 than in any of the preceding fifty-five years, whilst in 1945 and 1946 the rate of retirement of women from the service on health grounds was higher than for fifty years previously. There may be adequate reasons to explain these disturbing phenomena, such as the increasing age of the male employees, but it would be unwise to try and explain them away too facilely.

### THE BRITISH ASSOCIATION

Although the British Association does not attract the attention it did in the early years of the century, its annual meetings still subserve a useful function in publicizing science. At the meetings held in Brighton last month, one of the major items of medical interest was Sir Rock Carling's brilliant defence, before a joint meeting of the physiology and psychology sections, of the "over-sixties". Pointing out that the acceptance of 60 to 65 as the retiring age had no scientific basis, he urged that the time had come to combat this idea resolutely in the interest of individual health and happiness as well as of national advantage.

Another interesting discussion from the medical point of view was one devoted to an analysis of the emotional reactions of 400 adolescents to the cinema. This showed, among other things, that of all those between the ages of 13 and 16, 60% visited the cinema at least once a week; 17% reported that they were shocked by what they saw.

Doctors are often accused of being unnecessarily conservative in their habits, particularly where the adoption of the metric system is concerned. It was therefore comforting to learn that the engineers attending the meetings were sharply divided on the subject of the universal adoption of the system.

WILLIAM A. R. THOMSON

London, October, 1948.

# ABSTRACTS FROM CURRENT LITERATURE

## Medicine

**The Use of Vitamin E in Heart Disease.** Baer, S., Heine, W. I. and Gelfond, D. B.: *Am. J. M. Sc.*, **215:** 542, 1948.

The work on vitamin E in the treatment of cardiac disability which has received wide publicity in this country has led these authors to try its effect on 22 cases of cardiac disorder. The series was composed of 11 cases of congestive heart failure, 5 of angina pectoris and 6 with hypertensive, arteriosclerotic heart disease.

Of the 11 cases of congestive heart failure, 3 showed improvement while receiving the drug but in each case there were other factors operative which might have been responsible. One case discontinued her factory employment at about the time when improvement appeared; the remaining two displayed reduction in symptoms with placebos comparable with that obtained following the administration of the vitamin. Eight cases were either not improved or became worse.

Of the 5 cases with angina pectoris one showed "possibly a slight decrease in the frequency of anginal seizures"; a second showed some slight improvement but this occurred coincidentally with the arrival of milder weather. The remaining 3 cases were either no better or become worse while under the therapy.

In the 6 hypertension-arteriosclerosis cases there was no improvement which was not duplicated on exhibiting a placebo. There was no definite alteration of blood pressure and no change in ECG findings occurred which could be directly attributed to the drug. There was no reduction in x-ray size of the heart.

The authors conclude that their experience does not recommend the use of vitamin E in the treatment of angina pectoris, congestive heart failure or hypertensive disease.

G. A. COPPING

**Vitamin E in Heart Disease.** Levy, H. and Boas, E. P.: *Ann. Int. Med.*, **28:** 1117, 1948.

Vitamin E in very large doses was administered to 13 patients who were examined carefully at regular intervals to determine whether any subjective or objective changes followed the use of this substance. In some, control levels of a-tocopherol were taken and these showed normal values for the level of this vitamin. Absorption of the drug was excellent in all those whose plasma levels were tested and the values roughly paralleled the dosages. Aside from symptoms of headache, dizziness and vertigo on the higher dosages, there was remarkably little change or effect from this drug. In particular, there was no evidenue of diuresis or amelioration of the symptoms or signs of chronic heart failure in the five cases studied. Nor was there any evidence whatsoever that this drug affected the pattern, the frequency, the intensity, or the precipitation of anginal pain with a stable pattern of chest pain related to effort. Likewise, in three cases of active angina pectoris, in states of coronary insufficiency, characterized by a new pattern of increased frequency and intensity of attacks, often occurring at complete rest, there was no change to be attributed to the use of this vitamin.

The authors found no clinical evidence to warrant the use of vitamin E in the types of heart disease discussed.

S. R. TOWNSEND

**Thrombosis as a Complication of Internal Diseases.** Kallner, S.: *Arch. Int. Med.*, **81:** 126, 1948.

Thrombosis and thrombophlebitis, for many years considered independent diseases and the responsibility of the surgeons, are now being regarded more and more as frequent complications of such diseases as pneumonia, bronchopneumonia, cardiac disease and anæmia. Cases have occurred where pneumonia did not respond to chemotherapy and where after the fever had continued for some days a fatal pulmonary embolism, proved at autopsy to come from thrombi in both legs, explained the temperature. This is not as uncommon a complication as has been believed. Small pulmonary emboli could very well be the cause of the blood-streaked sputum reported so often in pneumonia. This suggests the use of anti-coagulants in all cases of pneumonia where the temperature does not return to normal when it ordinarily would. Cases are reported where the administration of dicumarol, caused a speedy end to a persisting temperature and rapid recovery. It is recommended to begin with heparin and continue with dicumarol, also to encourage movement of the patient in bed and use some massage.

This technique has also been used with benefit in cardiac infarctions, anæmia and parturition, even where a thrombosis has been present. A case is reported where transfusion sensitization had caused anuria and jaundice, etc., and heparin cleared up the picture very rapidly. Again fibrinous bronchitis producing respiratory embarrassment has responded to ephedrine or adrenalin, along with heparin.

P. M. MACDONNELL

**Treatment of Migraine with Histamine.** Macy, D. and Horton, B. T.: *J. Am. M. Ass.*, **137:** 1110, 1948.

Histamine has been reported to have prophylactic and curative effect on migraine. This drug has been used in the treatment of migraine at the Mayo Clinic since 1937. Five factors are fundamental to this syndrome. (1) Periodicity. (2) Cephalalgia. (3) Gastrointestinal dysfunction. (4) Cortical disturbance. (5) Familial history of migraine. For this study only those cases were selected in which both periodicity and cephalalgia were present in addition to any one or more of the remaining factors; 144 migrainous patients were treated with histamine alone at the clinic between the years 1937 and 1945. From 23 to 33% of the patients were unchanged after histamine therapy irrespective of the route of administration. Of the 88 patients who exhibited the improvement during the period of treatment and concerning whom follow-up data were complete, 85 experienced a recurrence of migrainous attacks when histamine therapy was decreased below an individual critical level or was stopped entirely. The 3 patients whose migrainous attacks did not recur were still taking histamine at the time of their reports. A tendency was noted for typical migraine to be more refractory to treatment with histamine and to recur sooner after such treatment than atypical migraine. The impression was that fairly satisfactory control of migraine attacks could be maintained either by intravenous or subcutaneous administration of histamine, however, if the histamine was discontinued, there was almost a universal recurrence of the attacks.

J. PRESTON ROBB

**The Leukocytosis of Diabetic Acidosis.** Tullis, J. L.: *Am. J. M. Sc.*, **215:** 424, 1948.

The leucocytosis which occurs during diabetic coma has never been satisfactorily explained. It is known that in experimental animals increasing the concentration of the extra-cellular fluids leads to a polymorphonuclear leucocytosis. In an attempt to see whether the white cell response during diabetic coma was accompanied by corresponding changes in tonicity of the extracellular fluids, the findings in diabetic coma were studied. There was demonstrated to be a direct linear relation between the level of the white blood cell count and the concentration of the extracellular fluid in seven cases studied. It is of interest that in the experimental animals the tonicity increase of the extracellular fluid which produced the leucocytosis was due to sodium chloride while in the cases of diabetic coma it was due not to that salt but to the combined effects of sugar, urea and ketone bodies. That the same ultimate effect is produced by dissimilar agents would seem to bear out the assumption of the importance of tonicity change rather than to suggest the importance of variations in any individual chemical entity.

G. A. COPPING

**Benign Idiopathic Spontaneous Pneumothorax. A Review of 63 Cases.** Hyde, B. and Hyde, L.: *Am. J. M. Sc.*, **215:** 427, 1948.

The authors have collected together 63 cases of this condition and present a statistical survey of their findings. Stated briefly the conclusions to be drawn from the figures are that the disease is primarily one of thin, young, adults with chest pain as its most frequent clinical feature. In the authors' experience the association of the onset of the attack with physical effort was unusual. There were no cases presenting pleural adhesions, a finding in striking contrast to the frequency of that feature in those cases of known active pulmonary tuberculosis who develop spontaneous pneumothorax. About a third of the cases showed pleural fluid; in only two was the amount sufficient to require thoracentesis and in one frank blood was aspirated. In the opinion of the authors the occurrence of large amounts of pleural fluid should be taken as a warning of the presence of possible tuberculosis.

The time taken for expansion was followed and it was found that the same percentage of collapse might take greatly different time for recovery in different patients. The factor of recurrent leakage or further brisk air entry into the pleural space was always an inestimable factor in assessing prognosis. The authors' view regarding the time at which it may be considered safe to allow these patients up and about is that they may have bathroom privileges when the lung has re-expanded to 80 or 85% of its volume. Of the 63 patients, 18 were carefully followed for periods of from 1 to 8 years without the appearance of any evidence of tuberculosis.

G. A. COPPING

**Aggressive Behaviour—Its Psychiatric and Physiologic Aspects, Especially in Combat Veterans.** Alexander, L.: *New England J. Med.*, **239:** 10, 1948.

Abnormal aggressive behaviour, of an asocial type, is a consequence of anxiety but may not be purely psychologic in origin. Various physiologic factors such as the action of drugs (especially alcohol) and exposure to extremes of temperature may upset the function of the cerebral cortex and give rise to examples of serious aggressive behaviour. Such possible factors should be considered when dealing with such patients.

NORMAN S. SKINNER

**Clinical Aspects of Carcinoma of the Cæcum and Ascending Colon: Report of 60 Cases.** Brown, C. H., *et al.*: *Ann. Int. Med.*, **28:** 940, 1948.

Sixty case histories of carcinoma of the cæcum and ascending colon have been analyzed. Pain was the predominant presenting symptom, being present in 76% of the patients. Many patients had symptoms of obstruction, with cramps and colic (38%) and vomiting (21%). Diarhœa was present in only 20% of the authors' cases. The average duration of symptoms before surgery was six and one-half months; 79% of the patients had an anæmia with less than 13 gm. hæmoglobin, but only 54% had less than 11 gm. Pathologically the most noteworthy findings were that 32% had an annular type of growth, and 25% had a constricting and obstructive lesion. The immediate post-operative mortality in the last five years has been 8%, two of 24 cases. One of these two cases was a poor renal risk and died from postoperative uræmia; 71% of these cases with no evident metastatic lesions at operation were living after an average follow-up of 3.8 years; 29% of those with metastatic lesions were living after an average follow-up of four years.

S. R. TOWNSEND

**Excessive Hypertension of Long Duration.** Burgess, A. M.: *New England J. Med.*, **239:** 75, 1948.

Hypertension is not as serious a condition as it is generally considered to be. Most prognostic studies have failed to properly separate the malignant from the non-progressive forms of the disease and hence have given a gloomier over-all outlook than is warranted. The question of prognosis in hypertension will not be satisfactorily settled until large groups of patients have been followed over long periods of time.

The author reviewed the records of his private patients dating back to 1914 and chose the first 100 cases in whom hypertension had been known to exist for a period of at least eight years. Eight years of non-progressive hypertension was regarded as evidence that malignant hypertension would not supervene. A systolic pressure of 180 or a diastolic pressure of 100 was selected as indicating hypertension. The average life expectancy of the entire group closely approximated the normal and since 47 patients are still living this factor will show further improvement with passage of time. Systolic hypertension by itself, even when extreme, appeared to have no prognostic significance. Diastolic hypertension was of much more importance. Life expectancy was less the younger the age at which the hypertension developed but since the average duration of life of the patients in this group under the age of fifty was eighteen years the author questions the value of sympathectomy in non-malignant forms of the disease.

NORMAN S. SKINNER

**Experience with the Schemm Regimen in the Treatment of Congestive Heart Failure.** Newman, A. A. and Stewart, H. J.: *Ann. Int. Med.*, **28:** 916, 1948.

The diuretic effect of the Schemm regimen, consisting of a high fluid intake and a low sodium, neutral or acid ash diet, was analyzed in nine patients suffering from congestive heart failure. Thirty additional patients were not used in the final analysis because they lost the signs and symptoms of heart failure during the control period, or because of the occurrence of events while on the Schemm regimen which invalidated inferences about the usefulness of the regimen.

Of nine patients, eight failed to have a beneficial effect when the regimen was used alone, without the addition of mercurial diuretics, in conjunction with the high fluid intake. In three patients no clinical improvement and no change in weight occurred. In six trials in six patients there was gain in weight, and fluid accumulations appeared to increase. In one patient with minimal œdema, weight loss occurred, although definite clinical improvement was not apparent. The average daily fluid intake for each patient ranged from 3,000 to 5,000 c.c. Five patients experienced difficulty taking this amount. Discomfort from the large water intake, or interference with consumption of the diet, constituted the major difficulties. Two patients experienced no difficulty with the high fluid intake, and there were no instances of untoward reactions.

The low sodium, acid ash diet formulated by Schemm was not liked by the majority of the patients. They considered it inferior to the standard three-gram salt diet in palatability and choice of food. The limited selections of fruit and vegetables were the main undesirable features.

Isolated instances of marked diuresis were encountered when mercupurin was used in conjunction with the Schemm regimen. This was followed, however, by fall in the urine output to its lower levels, and in the long run the removal of fluid was not materially affected. In general the results obtained with the use of mercurial diuretics in association with the regimen were not sufficiently uniform or consistent to give the impression that mercurials were more effective when used in conjunction with this regimen, than with the low salt-low fluid regimen. In all patients in whom the Schemm regimen failed to produce a satisfactory response, it was observed that the daily urine output failed to approach the amount of fluid intake. Many cases were found unsuitable for trial with the Schemm regimen. Of 30 cases originally studied, only nine could be considered suitable for analysis, and of these, at least half developed complications which interfered at some time with the proper maintenance of the regimen. Ascites proved to be the most difficult manifestation of heart failure to treat.

Seven of the nine patients proved better on the usual regimen of restricted salt and limited fluids with frequent administration of mercupurin, than they did on the Schemm regimen when fluids were forced and no diuretics were given. S. R. TOWNSEND

**Inhibition of Hair Growth by the Percutaneous Application of Certain Adrenal Cortical Preparations.** Whitaker, M. L. and Baker, B. L.: *Science*, **108**: 201, 1948.

Studies undertaken and reported during the past 15 years have produced evidence suggesting that the adrenal cortex may act as an inhibitor of hair growth. Regrowth of hair on depilated areas of adult rats was accelerated by adrenalectomy. Melanin deposition in hair was also stimulated by adrenalectomy under conditions ordinarily inhibitory of such production. Injected desoxycorticosterone acetate and to a lesser degree adernal cortical extract prevented the above effects which followed adrenalectomy. Such observations pointed to the cortical part of the gland as being responsible for these effects. In order to determine whether or not adrenal cortical preparations might exert an inhibiting influence on hair growth when applied directly to the skin, the authors, working in the Department of Anatomy, University of Michigan, treated depilated areas on one group of rats with adrenal cortical extract and a second group with 11-dehydro-17-hydroxycorticosterone while a control group was treated with 25% alcohol. The greatest inhibition of regrowth was observed in the animals treated with the purified cortical hormone, but no change in the rate of hair replacement occurred in the animals treated with alcohol. The test substances were applied directly upon the skin and rubbed in lightly. The conclusion from the observations was that at least one of the 11-oxysteroid hormones, which is the group known to exert a gluconeogenic action in general metabolism, can exert a direct depressing effect on growth of hair in the rat. The action was local, not by intermediation of any known endocrine gland, and hair follicles not directly treated remained unaffected. D. E. H. CLEVELAND

## Surgery

**A Review of Surgical Methods in the Treatment of Essential Hypertension.** McGregor, A. L.: *Brit. J. Surg.*, **35**: 281, 1948.

Chiding British surgeons on their conservatism, this Johannesburg surgeon reviews his first 50 private cases and discusses the case for surgery for hypertension. He leans toward the theory that the disease is basically neurogenic, and that the stimuli from the brain can be interrupted by splanchnicectomy. Later the kidneys changes become irreversible and the blood pressure remains high after the operation. Medical and surgical measures should be used as complementary methods of treatment.

Craig, Adson, Crile and Peet pioneered in sympathectomy for hypertension, and Smithwick originated the operation which the author uses: lumbo-dorsal ganglionectomy with splanchnicectomy. The mortality of this two-stage procedure is low and 80% of the patients show a worthwhile fall in the resting diastolic pressure, 90% obtain relief of symptoms. In a high percentage of cases the damage to eye grounds, myocardium and kidneys is reversible by operation.

The evaluation of the case of hypertension is described. The young hypertensive will do well, and the old arteriosclerotic does poorly, but there are many in the intermediate group who present a problem as to whether or not surgery should be advised. Max Peet is quoted regarding the criteria for operation: under 54 years of age; continuously elevated blood-pressure, with systolic pressure over 170 and diastolic pressure above 105; a non-protein nitrogen below 45 mgm.; a relatively well-compensated heart and a relatively normal cerebral function. Cases of malignant hypertension have been followed and are well up to eleven years after operation. The papers of Smithwick are recommended.

The operations are carefully described, with diagrams of special instruments and coloured plates. Postoperative care is important since the blood pressure may be very low. Prophylactic penicillin is given. The patient is up on the 3rd day. The operations are 10 days apart and he is out in 4 or 5 weeks. Supports to the legs and abdomen are worn for at least 3 months. Renal biopsy is usually done. BURNS PLEWES

**Studies on Vagotomy in the Treatment of Peptic Ulcer.** Meyer, K. A., Rosi, P. A. Stein, I. F.: *Surg., Gyn. & Obst.*, **86**: 524, 1948.

Following the work of Dragstedt, 35 patients who had been subjected to vagotomy for duodenal or stomach ulcer were studied. The last 26 cases were done by the transabdominal approach, and this is preferred because there is less likelihood of missing some vagus fibres, the lesions can be inspected, convalescence is easier and quicker, a gastroenterostomy may also be done. In about 8% of cases complete vagus resection is difficult to achieve. Gastric decompression should be maintained for at least 5 days and patients were warned against overeating for a few months. The clinical results were excellent. Thirty-one of them lead an unrestricted life. Thirty had a good weight gain. One died as a result of a transfusion reaction. Foul eructations lasted 5 months but then ceased in one case, and two had diarrhœa for two months. Three patients had cardiospasm for 1 to 3 weeks. One still has loss of appetite and one has occasional vomiting.

Nevertheless, it is stated that it is too early to evaluate vagotomy for peptic ulcer. It should be limited to clinical investigation with one exception: it is the method of choice in the treatment of marginal ulcer following gastric resection. BURNS PLEWES

**Studies on Vagotomy in the Treatment of Peptic Ulcer.** Stein, I. F. and Meyer, K. A.: *Surg., Gyn. & Obst.*, **87**: 188, 1948.

In a study of 30 patients before and after vagotomy for duodenal ulcer, it was concluded that the vagi are the sole mediators of the cephalic phase of gastric secretion. There is a marked reduction of night secretion and of the basal secretion. The secretory response of the stomach to caffeine and histamine is greatly reduced. Normally insulin hypoglycæmia produces an increase in gastric and motility. This is abolished by vagotomy so that there are no spontaneous hunger contractions in the stomach up to 9 months after the operation. Complete vagus section in some manner interrupts a mechanism necessary for the chronicity of peptic ulceration. BURNS PLEWES

## Obstetrics and Gynæcology

**Retreatment of the Pregnant Woman for Syphilis Following Penicillin.** Ingraham, N. R., Rose, E. K., Stokes, J. and Berman, H. in collaboration with Wammock, V. S., Handler, S. H. and Carrozzino, O. M.: *Am. J. Obst. & Gyn.*, **56**: 340, 1948.

When 52 women were treated for syphilis with penicillin before but not during pregnancy, 46 apparently normal and no syphilitic living infants resulted. The three abortions, one miscarriage and one neonatal death which occurred could not be attributed to syphilis, and probably resulted from other causes. So far as can be told from a limited series of cases, retreatment during pregnancy for syphilis is unnecessary, provided that the expectant mother's response to previous penicillin therapy has been normal and reinfection has not occurred.

Criteria are given for the selection, based upon clinical response of patients in whom retreatment for syphilis because of pregnancy may be unnecessary, but the possible fallacy of basing judgment solely on the clinical response in the individual case is pointed out.

The great effectiveness and relative safety of penicillin to prevent congenital syphilis make retreatment of the pregnant woman desirable if there is any doubt whatever of the effectiveness of her previous antisyphilitic therapy. ROSS MITCHELL

**The Application of a Silver Carbonate Stain for the Diagnosis of Uterine Cancer by the Vaginal Smear Method.** Yue, H. S., Riley, G. M., Miller, N. F. and Scharenberg, K.: *Am. J. Obst. & Gyn.*, **56:** 468, 1948.

The silver carbonate staining method of Hortega was modified for staining the cellular elements of vaginal smears. The details of the procedure are described. The affinity of chromatin material for the silver stain, together with the usual hyperchromatic character of atypical cells, combine to make this a useful stain in the diagnosis of uterine cancer by the vaginal smear method. The cytoplasmic and nuclear characteristics of cells impregnated with silver carbonate are described and several noteworthy advantages of the technique over other conventional stains are listed. ROSS MITCHELL

**Oxidized Cellulose Used for Intrauterine Postpartum Packing.** Anderson, H. E., McIntyre, A. R., Reaney, B. V. and Taylor, W. H.: *Am. J. Obst. & Gyn.*, **56:** 391, 1948.

Oxidized cellulose in long strips was used as a postpartum intrauterine pack in twenty-four patients, of whom three demonstrated frank postpartum hæmorrhage. Results obtained indicated that this type of packing is effective in the control of bleeding and has no harmful effects, either locally or generally. The gauze is spontaneously expelled by the uterus too soon to allow for complete absorption. This study serves to demonstrate that the gauze can be safely introduced into the postpartum uterine cavity to control postpartum bleeding. This represents a preliminary report and a large number of cases are required for study before conclusions can be drawn. ROSS MITCHELL

**Theca-cell Tumours of the Ovary with a Report of Fifteen Cases and a Review of the Literature.** Knight, W. R.: *Am. J. Obst. & Gyn.*, **56:** 311, 1948.

Fifteen cases of theca-cell tumour of the ovary have been evaluated and presented with a survey of the literature and a clinical and pathological review. This series contained the largest theca-cell tumour yet reported, weighing 7,727 gm. (17 lb.). Biologic assay of this tumour revealed the equivalent of 0.2 gamma of œstrone per 100 gm. of extracted tissue. There was no progesterone in the tumour tissue and no pregnandiol excreted in the urine of the patient.

Although the œstrogen produced by thecoma is small, its effect is prolonged and unopposed by the action of progesterone, which may account for the symptoms and frequent occurrence of associated pathology, such as menstrual irregularities, post-menopausal bleeding, endometrial hyperplasia, adenomyosis, hypertrophy of the myometrium with uterine enlargement, uterine myomas and endometrial carcinoma. The collected evidence is not conclusive as to whether the theca-cell tumours represent a distinct histologic type of ovarian neoplasm and the subject warrants further study, since the active endocrine principle of both theca-cell tumour and granulosa-cell tumour is œstrogen. Theca-cell tumours occur most frequently in the fifth and sixth decades with 61.5% of our patients past 50 years of age. Uterine curettage should be done in all cases to rule out associated adenocarcinoma of the endometrium. Conservative surgery is the operative choice in the premenopausal patient in the absence of associated adenocarcinoma of the endometrium. In the presence of the latter, total hysterectomy is always the procedure of choice. The distinctive diffuse yellow colour seen on section of theca-cell tumours is the best gross diagnostic criterion and was present in 100% of our cases.

ROSS MITCHELL

**The Action of Intravenously Injected Sex Hormones.** Loeser, A. A.: *J. Obst. & Gyn. Brit. Emp.*, **55:** 17, 1948.

An instrument is described by means of which changes in blood-flow in the endometrium of the human uterus can be recorded. The method of using the apparatus is described. The effects of intravenously injected sex hormones and other substances on the endometrial blood-flow were studied. Natural œstrogens and to a less extent progesterone produce a vasodilator action; testosterone proprionate produces predominately a vasoconstrictor action. Stilbœstrol has a trifling dilator action. Adrenalin and pituitrin have a strong and lasting vasoconstrictor action.

P. J. KEARNS

**The Composition of the Blood of Women During Pregnancy and After Delivery.** Hoch, H. and Marrack, J. R.: *J. Obst. & Gyn. Brit. Emp.*, **55:** 1, 1948.

The mean concentration of hæmoglobin fell as pregnancy advanced; the globin curve was similar to that found by others. The mean concentration rose after delivery. The mean concentration of iron in serum did not change during pregnancy; it bore no relation to the concentration of hæmoglobin. The total serum protein fell as pregnancy advanced; the serum globulin remained approximately constant; the curve of fall of serum albumin was roughly parallel to that of hæmoglobin. The non-protein nitrogen in serum was low from the earliest stages of pregnancy and rose after delivery. The mean concentration of vitamin A in serum was below the level found among non-pregnant women. No significant change occurred after delivery, when the concentration rose to the mean level found among non-pregnant women. The concentration of vitamin A and ascorbic acid in sera of women taking vitamin supplements were higher than in the sera of those who were not taking these supplements, but the highest mean concentrations of ascorbic acid in serum were found in those months in which the amounts in the diet are highest. P. J. KEARNS

**Demonstration by Infra-Red Photography of the Superficial Veins in the Pregnant and Non-pregnant Women.** Bowes, K., Riterband, S. H. and Andrews, J. E.: *J. Obst. & Gyn. Brit. Emp.*, **55:** 285, 1948.

The breast veins as a physical sign of pregnancy and an aid to diagnosis. Encouraged by the very definite contrast seen under favourable circumstances between the photographs of the veins of the breast in the pregnant and non-pregnant patients, a series of photographs was taken of patients attending the antenatal and gynæcological clinics to see if sufficient accuracy could be attained to establish a diagnosis or not of pregnancy. If the changes fully typical of pregnancy were present, *viz.*, increase in density and lumen of veins, development of the mosaic patterns of collateral circulation, and/or the enlargement of the circumareolar veins, a full "positive" diagnosis was given. Not infrequently, particularly in abortional patients, changes suggestive of pregnancy, but not fully definite, were found. P. J. KEARNS

**Evolution and Growth of Tadpoles by Feeding Vernix Caseose Progesterone and Folliculin.** Lajos, L. and Szontagh, F.: *J. Obst. & Gyn. Brit. Emp.*, **55:** 281, 1948.

Our results seem to show conclusively that while vernix caseosa promotes growth and metamorphosis, progesterone acts only on growth, and folliculin has no obvious effect. The fat-content of vernix as a possible cause could be excluded and the same could be said of folliculin, although the data of earlier investigators in this respect are somewhat contradictory in this respect. It is known that thyroid feeding accelerates metamorphosis and inhibits growth, and thymus promotes growth and inhibits metamorphosis. Addition of 10% vernix to the food of tadpoles is followed by a marked

acceleration of growth and metamorphosis. Progesterone promotes growth, but has no effect of metamorphosis. Folliculin or fat feeding has no definite effect on either.

P. J. KEARNS

**Hydatidiform Mole in the Fallopian Tube.** Chalmers, J. A.: *J. Obst. & Gyn. Brit. Emp.*, **55:** 322, 1948.

The literature relating to hydatidiform mole of the Fallopian tube is reviewed and a further case described. This brings the total number of cases recorded to 15. The Aschheim-Zondek reaction is not of value in distinguishing between tubal pregnancy with a normal ovum, and that with a hydatidiform mole. The treatment is that of any tubal pregnancy but careful follow-up with biological tests is demanded to exclude subsequent malignant degeneration. The prognosis is good and better relatively than in uterine hydatidiform mole where the uterus is ordinarily left *in situ*.

P. J. KEARNS

**Hysterosalpingography Employing a Water-Soluble Contrast Medium.** Jeffries, D.: *J. Obst. & Gyn. Brit. Emp.*, **55:** 270, 1948.

Twenty-four infertile women have been subjected to hysterosalpingography with pyelosil after the male partners had been found normal. The results are listed below.

YEARS OF INFERTILITY

| | *State of tubes* | |
|---|---|---|
| | *Patent* | *Blocked* |
| Under 5 years | 14 | 2 |
| 5 to 10 years | 5 | 2 |
| 10 years or over | 0 | 1 |
| Total cases | 19 | 5 |

This also gives the duration of infertility based on the years of effective marriage; periods when contraceptives have been used or when one or the other partner has been absent have been subtracted from the actual years of marriage.

The figures show (1) patent tubes, (2) hydrosalpinx, (3) pyosalpinx, and (4) obstruction at the ampullary end (later shown to be due probably to spasm). Of the 5 cases of obstruction 3 patients have so far been submitted to laparotomy and have shown anatomical obstruction due to pyosalpinx in 2, and tuberculous salpingitis in one.

P. J. KEARNS

## Anæsthesia

**Complications of Anæsthesia in Pædiatrics.** Smith, R. M.: *Current Res. Anæsth. & Analg.*, July-August, 227, 1948.

This report is based on a survey of 6,616 consecutive anæsthesias given over 18 months' period at The Children's Hospital, Boston. The series includes 127 major intrathoracic operations. In comparing the complications of anæsthesia in pædiatrics with those of anæsthesia for adults it is apparent that there is a similarity in nature of complications but a marked difference in the rate and time of incidence. Anoxia is the greatest single danger in anæsthesia in pædiatrics as it is with adults, but the effects are manifested more quickly. Apnœa, shock and pulmonary œdema will occur rather than such delayed effects as hypostatic pneumonia or atelectasis.

Inadaquate premedication will result in a stormy induction of anæsthesia followed by irregular, gasping respiration often continuing throughout the remainder of the operation. Poorly medicated patients are also more prone to vomit during induction. Irritating anæsthetic induction agents often produce dangerously long periods of breath holding. A loosened deciduous tooth is frequently aspirated causing respiratory obstruction.

Intubation of infants does not give the anæsthetist the same assurance as intubation of adults, as the calibre of the tube is of necessity so small that only a few drops of mucus are enough to obstruct it. It is also very easy to push the intratracheal catheter in too far, beyond the carina into one of the bronchi; thus obstructing half of the respiratory passageway.

In children under anæsthesia, circulatory disturbances are less frequently encountered than respiratory abnormalities. However it has been determined that in children, morphine, when used with cyclopropane anæsthesia, increases the occurrence of cardiac arrhythmia. Lack of consideration of conservation of fluid loss and changes in body temperature may be the cause of many complications during and after operation. Infants are quick to suffer from loss of even small amounts of fluid and it is difficult to start an infusion on a 4 pound infant halfway through an operation. The postoperative period in children is, as a rule, gratifyingly free of major anæsthetic complications. Respiratory depression, especially after chest operations, is most common. The rare cases of postoperative pneumonia occur chiefly as a result of aspiration.

F. ARTHUR H. WILKINSON

## Neurology

**Electroencephalographic Studies in Poliomyelitis.** Goldbloom, A., Jasper, H. and Brickman, H. F.: *J. Am. M. Ass.*, **137:** 690, 1948.

Abnormalities in the electroencephalogram were found in a large proportion of patients following poliomyelitis. These changes were much more common in children than in adults. Partial and complete recovery was observed in some patients during a period of five to eight months following the acute illness. In others, there was evidence of persistent abnormality in the electroencephalogram for at least five to fifteen years. It was concluded that cerebral involvement in poliomyelitis was much more common than would be apparent from clinical observation alone. Correlation between the development of disturbed behaviour and abnormal electrical activity following poliomyelitis was high, with ten out of eleven patients with severe behaviour disturbances showing abnormal electrograms. There was no correlation between mild personality disorders and electroencephalographic disturbances. This finding was compatible with the well known complexity of etiologic factors influencing behaviour following poliomyelitis. One would not expect to find a close correlation between the electroencephalographic and behaviour disorders. The latter are largely conditioned by environmental situations and the disturbance in cerebral function reflected in the electroencephalogram may not be of a type which affects behaviour in this sense.

PRESTON ROBB

**Oral "Myanesin" in Treatment of Spastic and Hyperkinetic Disorders.** Berger, F. M. and Schwartz, R.: *J. Am. M. Ass.*, **137:** 772, 1948.

"Myanesin" has a relaxant effect on muscle spasm, spasticity and rigidity and an ameliorative effect on tremor and involuntary movement of extrapyramidal origin. These effects are caused by a selectively depressing effect of the drug on the central nervous system. Up to the present, the drug has been administered intravenously and was thought to have little practical interest because of the evanescent action and side effects introduced with this route of administration.

The authors have shown that myanesin on oral administration produces most of the beneficial effects observed after intravenous administration without any of the side effects. The drug was well tolerated over a period of many weeks and favourable results were seen in many previously intractable conditions.

The drug was administered in 3.3% solution in 20% aqueous propylene glycol with a syrup of cherry 20% to improve the taste of the mixture. The usual single dose was 30 c.c. of the mixture equal to 1 gram of myanesin. Children received proportionally small doses. Hemiplegic patients, whose paralysis had been

stationary for four to seven years showed a striking recovery of some of the voluntary movements of the paralyzed limbs ten to twenty minutes after administration of the drug. The maximum benefit was usually obtained after two to three days of medication. Remarkable results were also obtained in certain cases of cerebral diplegia. The drug appeared effective in spastic athetoid and choreiform types of the disease. Some cases of Parkinson's syndrome were improved.

The oral administration of myanesin rarely caused side effects and in the cases observed there were no toxic reactions as had previously been reported with the administration of the drug intravenously. This drug may be a very useful adjunct to physiotherapy in the treatment of spastic conditions of neurological origin.

PRESTON ROBB

**Problem of the Congenitally Deaf Child.** Macfarlan, D.: *J. Am. M. Ass.*, **137:** 774, 1948.

This brief article summarizes the modern treatment of the congenitally deaf child. It outlines the important advances that have been made in this field with the advent of hearing aids. The little child deaf at birth or deaf before the age of two does not learn language with speech. Most of these children have usable hearing that can be reached by amplified sound. In a series of fifty patients, examined over two years, the author found that approximately 90% had usable hearing. Most of them could be taught to understand the spoken word by hearing aids and could be taught to speak intelligibly. The hearing aid should be tried even on the apparently hopelessly deaf child. Training in a conditioned response will not only improve the behaviour and attention but will permit a quantitative hearing test. Lip reading should be avoided.

It is highly advisable to prepare these children to enter the school for children with normal hearing, avoiding institutionalizing if results warrant it. Normalcy in growing up is most needed in any handicapped child. The case should be carefully followed by the physician to safeguard the hearing that remains, and to see that the language and speech training program is conscientiously carried out.

PRESTON ROBB

## Dermatology

**The Kveim Test in Sarcoidosis. The Theory, Meaning and Practical Value of Skin Tests in Sarcoidosis.** Leider, M. J.: *J. Invest. Dermatol.*, **10:** 377, 1948.

The 3 principal contending theories as to the cause of sarcoidosis are (1) it is a rare form of non-caseating tuberculosis; (2) it is a disease *sui generis* caused by a filterable virus; and (3) it is a type of pathologic tissue reaction which can be elicited by a variety of living and some non-living agents. The author believes that the concept of J. Jadassohn and his school, of specific positive relative anergy to tuberculin in sarcoidosis, hence evidence of its relationship to tuberculosis, is confirmed by the Kveim reaction. The apparent paradox of interpreting a negative finding such as Jadassohn's as proof of relationship is resolved by the existence of tuberculin anergy in sarcoidosis in an age group which normally should show a positive reaction to 1:5,000 Koch's old tuberculin, whether or not active tuberculosis is present. The unusual specific altered reactivity implicates tuberculosis rather than denying it. Otherwise to interpret it as exculpating tuberculosis it would be necessary to postulate that persons with sarcoidosis have never been exposed to or infected with tuberculosis. It was found that in the group of cases studied, those who had once been tuberculin positive and had, having developed sarcoidosis, become anergic to tuberculin could not again be sensitized by B.C.G. inoculation. Such specific, positive or acquired anergy is not the equivalent of the non-infected state but on the contrary related to, dependent upon or proof of a previous sensitization through exposure to tubercle bacilli. Kveim took up the problem of a skin test in sarcoidosis, thinking of it as a disease *sui generis* of virus causation, and concluded that his test was specific and allergic evidence that sarcoidosis was a disease entity. It remained for subsequent workers, including the author, to see it as adding to the evidence in favour of the relationship of sarcoidosis to tuberculosis.

The method of preparation of the antigen, making and interpreting the Kveim test is described in detail.

D. E. H. CLEVELAND

**Treatment of Chronic Ulceration of Postradiation Scar Tissue by Local Infiltration of Aqueous Solution of Penicillin.** Lamb, J. H. and Boyer, H. L.: *J. Invest. Dermatol.*, **11:** 3, 1948.

It is considered that the ulceration process is probably due largely to low-grade infection, favoured by poor nutrition and insufficiency of blood-borne antibodies consequent upon the poor vascularity of the postradiation scar. The antibiotic effect of penicillin appears adequate to combat ordinary pyogenic infections under these conditions. The area treated is first anæsthetized by infiltration with 1% procain. This is followed immediately by infiltration of the entire area with calcium penicillin in normal saline, 50,000 units per c.c. and using approximately 0.5 c.c. for each cubic centimetre of affected tissue. From 1 to 5 injections were given at approximately weekly intervals. The average time for healing was 26 days. This is a preliminary report based upon experience with 10 cases in which there was one failure.

D. E. H. CLEVELAND

**Sensitization to Monoglycerol Para-aminobenzoate. Preliminary Report.** Baer, R. L. and Meltzer, L.: *J. Invest. Dermatol.*, **11:** 5, 1948.

Since the discovery of the sunburn-protecting effect of para-aminobenzoic acid (see abstract in *The Canadian Medical Association Journal*, May, 1948) this chemical has been much used for this purpose and it is contained in certain proprietary preparations which are widely sold. The authors have published a timely observation of an allergic eczematous contact-type dermatitis due to this chemical in a proprietary preparation which occurred twice in a male patient. The etiology was proved by patch-testing. The patient had reacted strongly on previous occasions to benzocain and also to a sulfonamide, and it was considered likely the reaction to monoglycerol para-aminobenzoate was evidence of cross-sensitization based on the original sensitization of two derivatives of aniline, namely benzocain and the sulfonamide.

D. E. H. CLEVELAND

## Industrial Medicine

**Heart Disease Detection in Pre-employment Examinations.** Kuechle, B. E.: *Am. Rev. Tuberc.*, **72:** 383, 1948.

That handicapped individuals can fill their place in industry was demonstrated during the recent war. Their production record was on a very high level when compared with supposedly normal workers; their standards of loyalty, concentration on the job, lower accident rates and reduced absenteeism were above normal expectancy. That industry is willing, and even enthusiastic to employ them, has been indicated. In this connection one of the major problems is the maintenance as useful productive members of society, of persons suffering from heart disease. Cardiacs can be employed and should be employed for their own well being. Recently it was reported that out of 2,081 patients, representing the entire enrollment of 10 adult cardiac clinics in New York City, 65% were doing some work, and of 543 who were under 35 years of age, 80% were productively employed.

In this article the author's opinion is presented on the importance of detecting possible unknown cardiac disease in workers, as given by him in a talk at a Conference on Heart Disease Programs. He stresses the

importance of a well-planned medical program designed to place present or prospective employees at jobs, where, in spite of handicaps, they will be able to work efficiently and safely. In his opinion the x-ray is extremely valuable as a screening or case-finding method in either heart disease or tuberculosis, since, with it, it is possible to examine large numbers of people in a short time. The Heart Advisory Committee of the Los Angeles County Tuberculosis and Health Association has reported that 2% of 70,000 miniature films showed abnormal cardiac shadows. It must be remembered though, that many cases of heart disease show no abnormality in the x-ray picture; this is particularly true where the disease is primarily of the coronary arteries without hypertension. In any survey the importance of the many cases that are found, must be considered, rather than the few that might be missed.

The x-ray will give suggestive or positive evidence in most cases of hypertensive or rheumatic heart disease, in many cases of arteriosclerotic heart disease and in a certain number of cases of syphilitic heart disease (aneurysms). Most of these abnormalities would be recognized by doctors trained in reading miniature films. Those individuals whose films show abnormal cardiac shadows are entitled to the full value of the information revealed by the survey. Industry also is entitled to it, at least when proved to be of positive significance to aid in the better placement of the individual.

MARGARET H. WILTON

**A Psychiatrist Looks at the Causes of Alcoholism.** Seliger, R. V.: *Indust. Med.*, **17**: 125, 1948.

That, in general, excessive dependent drinking is a frequent result of poor unsatisfactory emotional and other life-habits is the opinion of the author. In this article he discusses the causes of alcoholism, which he looks on as a major national health problem, from a psychiatric viewpoint. He stresses the fact that alcoholism is symptomatic of psychopathology, that the pathology may be primary, or secondary, that physical complications may be in the picture (organic brain damage or deterioration), and that in order to attempt to treat the patient it is necessary to know about his personality make-up, the presence of any major or minor psychiatric illness and his actual life-setting and circumstances. Not all alcoholics can be helped; neither are all alcoholics hopeless.

The chemical and physical effects of alcohol, the pathology of alcoholism, and the psychopathology are presented briefly. The author then summarizes the causes producing the symptom of alcoholism and the individual motives for excessive drinking. In dealing with alcoholics, thorough examination and understanding of the underlying personality illness or disorder, is necessary. The examiner must determine what type of psychiatric problem the individual presents; how much deterioration is present; how serious is the extent of the drinking and what type of treatment, including placement, offers the best chance at recovery. The goal of treatment is to teach the individual, who can be helped, to learn how to live without ever again using alcohol in any form. No one who has had an alcohol problem can ever again drink "socially"; he must be a total permanent abstainer. Individual therapy is valuable. The patient must want help or be guided to want help with all his heart. Full co-operation from the family is essential. In the author's opinion, society must now assume responsible action in curative facilities and in preventive educational measures. He suggests as the most practical working program for the community and the individual, information centres where problems of alcoholism could be referred, associated with treatment facilities to handle acute problems. Such psychiatric units should be adequately staffed with trained personnel under the supervision of a psychiatrist. Affiliated services would include farms where selected patients could receive psychotherapy and common-sense re-education in life; and protective institutional arrangements for the more seriously psychiatric types, including feeble-minded and psychopaths. MARGARET H. WILTON

**Illumination and Colour in Industry.** Birren, F.: *Sight Saving Rev.*, **17**: 217, 1947.

That good vision demands ample light and proper brightness contrast, the latter being made possible through the co-ordination of light and colour, is stressed in this article. The author first discusses briefly (1) the basic principle that the eye sees best where luminosity is uniform, (2) the advantages and disadvantages of direct and indirect lighting systems and (3) the importance of an intelligent consideration of colour. Then, drawing upon his own actual experience, he presents a series of elementary principles and simple observations in order to suggest how colour and brightness specifications may be intelligently written.

Uniform luminosity in the field of view may be said to be tolerable where brightness ratios do not exceed 1 to 10; severe contrasts in the major field of view should be avoided. A surrounding field darker than the brightness of the task is far superior to a lighter surround. Reference is made to brightness specifications that have been successfully applied in numerous plants, and to certain refinements as background shields, and end-wall treatments in medium tones. Machinery may be highlighted to reflect more light at important parts and concentrate the attention of the worker. The author stresses the need in industry of careful regard for use of colour on ceilings, walls, equipment and machines, and shows how psychologically colour holds a fair amount of magic. It can achieve remarkable results when strategically applied. It contributes to better visibility and to an agreeable and cheerful frame of mind.

As a means of identification in safety practice it serves a useful purpose. In this connection, a code developed by the author in co-operation with Du Pont and later accepted in part by the American Standards Association, includes the following features: Yellow (or yellow and black bands) becomes standard to mark strike-against, stumbling or falling hazards. Orange is standard for acute hazards likely to cut, crush, burn or shock the worker. Green is standard to identify first-aid equipment. Red is reserved entirely and exclusively for the marking of fire-protection devices. Blue is standard as a caution signal. White, gray or black are standard for traffic control and good housekeeping.

MARGARET H. WILTON

# OBITUARIES

**Dr. Walter Stewart Baird** died on September 11 in General Hospital, Vancouver. He was 65. Born near Lucknow, Ont., in 1883, Dr. Baird was a graduate of McGill University in 1907, interned at the Montreal General Hospital and came to Vancouver in 1911.

He was an officer in the Army Medical Corps in the First World War and entered the R.C.A.M.C. in the Second World War in June, 1940. He was commanding officer of Victoria Military Hospital from January, 1942, to August, 1943.

Following his retirement from the army, he was appointed assistant chief medical officer at Shaughnessy, later becoming assistant hospital superintendent. He is survived by his widow and one daughter, Mrs. Wm. C. Gibson.

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**Dr. Louis Berger,** of Laval University, died in hospital August 31. He was 53. Born in Strasbourg, France, Dr. Berger received his doctorate in medicine from the University of Strasbourg in 1924 and then moved to Canada. He became a member of the Laval teaching staff in 1925 and in 1928 founded, in co-operation with Dr. Arthur Vallée and Dr. Charles Vézina, an anti-cancer centre at the university. A few days before his death and while in hospital he was decorated with the Cross of Chevalier of the French Legion of Honour.

He is survived by his widow and a sister.

**Dr. G. C. W. Bliss,** medical health officer for the Town of Amherst, N.S., died at his home September 17. He was over 90 years of age and up to a few days before he was confined to his bed he had carried on his regular duties as a practitioner and until his illness was vigorous and active. He was a graduate of Jefferson University of Philadelphia and before taking up his medical studies had served with other doctors then practising in Amherst. Dr. Bliss was a native of Mount Whatley, near Aulac, and was a cousin of Sir Charles G. D. Roberts and poet Bliss Carman. He was a great patriot and was renowned as a sportsman and naturalist. He shot and fished over most of the Maritimes. He took an active part in combating epidemics in the town and county and was a firm believer in the modern toxoid clinics. Dr. Bliss took a prominent part in the affairs of Amherst in its early days. He was closely linked with the first fire department of the town and was also a member of one of the early bands. He belonged to the Amherst Rifle Club and various gunning and fishing clubs. He is survived by four sons and two daughters.

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**Dr. Ernest Bottomley** died in Smithers, B.C., on August 12, aged 79 years. He practised medicine at Dauphin, Man., for fifty years before retiring. He is survived by his son.

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**Dr. William J. Campbell** of Sudbury, Ont., died in the Copper Cliff hospital September 11. He was in his 62nd year. A native of Tweed, Ont., he graduated in medicine from the University of Toronto in 1911, and went to England for a postgraduate course. Later he joined the medical staff of the old Canadian Copper Company, now the International Nickel Company. Dr. Campbell practised at Creighton, Crane Hill, Frood and Copper Cliff. He lived at Copper Cliff for more than 20 years, prior to taking up residence in Sudbury in 1939. He was a member of the United Church and was associated with the Copper Cliff school board for several years. He was also a member of the Algonquin Lodge, A.F. & A.M., at Copper Cliff. Surviving besides his widow, are his mother, two sons, two grandchildren, and a sister.

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**Dr. James Winter Cartmell** died on August 25 at his home in Glenboro, Manitoba, in his 82nd year. Born at Listowel, Ont., he came to Birtle with his parents in 1880. He attended Manitoba University and graduated in 1891. He carried on his practice at Glenboro for 57 years. For 41 years he was medical health officer of the municipality of South Cypress and reeve for ten years. He took a keen interest in all public affairs and was an enthusiastic curler. He is survived by his widow, one daughter, one son, and one granddaughter.

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**Dr. M. F. Caverhill,** medical director of the Workmen's Compensation Board, died suddenly in Vancouver on September 18, at the early age of 37, of a heart attack. Dr. Caverhill was Executive Secretary of the British Columbia Medical Association before his appointment to the Workmen's Compensation Board and was intimately known to all the medical men of the Province. He enjoyed the respect and affection of all who came in contact with him, and his untimely death comes as a great shock to all his many friends.

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**Le Dr Donat Chrétien,** médecin en chef de la quarantaine du ministère de l'Immigration à Québec, s'est noyé le 19 septembre au large du hangar 18 dans le port de Québec, comme il quittait le "Quamadolake" pour prendre place à bord du "Salucan", le navire de la quarantaine. Une belle carrière au service de l'Immigration canadienne depuis 1928 se termine par ce tragique accident. Le Dr Chrétien était âgé de 53 ans. Il a servi successivement à Québec, en Europe, à Vancouver et Halifax, avant de revenir dans la Vieille Capitale. Il laisse sa femme, une fille, un frère, une sœur et sa mère.

**Dr. Frank R. Davis,** 60-year-old Nova Scotia health minister, died at Ingonish, N.S., on September 16. Born in Shelburne, N.S., he was a graduate of Mount Allison University of Sackville, N.B., and Dalhousie University. A physician and surgeon, he also was a director of General Trust and Executor Corporation and of Maritime Telegraph and Telephone Company. He was a Fellow of the American College of Surgeons. He was elected with the first Liberal Macdonald Government in 1933 and was appointed to the health portfolio the same year. He was re-elected in the general elections of 1937, 1941 and 1945 and was a member for the two-seat constituency of Lunenburg. Last September he took over the Ministry of Municipal Affairs. Surviving are his widow and two sons.

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**Dr. John James Davis,** aged 73, died on August 24 at his home in Gananoque. Born in Toronto, he received his early education in London, Ont., public and high schools and graduated in medicine in 1897 from the University of Western Ontario. He established a practice in Gananoque in 1907. Dr. Davis was a member of Leeds Lodge, A.F. and A.M.; past principal of Leeds Chapter, R.A.M.; past grand superintendent, St. Lawrence district, R.A.M.; member of Kingston Scottish Rite and most wise sovereign, Rose Croix, Scottish Rite. In 1934 he was made a 33rd degree Scottish Rite, an honour which also had been conferred upon his father. For a number of years he served on the school board and was a former chairman. He was a member and elder of St. Andrew's Presbyterian Church, and a charter member and past president of the Rotary Club. He leaves his widow, a son, a daughter and a sister.

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**Dr. John A. Ivey** died recently in Cobourg, Ont., in his 87th year. Born near Jarvis, he came to Cobourg as a youth and received his education at Cobourg Collegiate and Victoria College, going to Toronto for his degree in medicine. He practised for two months in Woodstock and then returned to Cobourg. He was responsible for the first hospital accommodation in Cobourg by securing, in the early 1890's, some rooms in the Old People's Home for use as an emergency hospital. Dr. Ivey retired in 1928, but always retained a keen interest in medical developments. He is survived by his widow, three daughters and a son.

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**Dr. Emile Alexandre Jeannotte** died in Montreal on September 14. He was in his 64th year. A native of St. Hilaire, he studied at Ste. Marie College and the Nicolet Seminary and later at the University of Montreal. He displayed great interest in free clinics and spent considerable time at the Ville Emard Clinic. He is survived by his widow, two sons, a daughter, a brother, and two sisters.

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**Dr. George Edward Kidd,** died on September 1 at at his home in Vancouver. He attended the Carleton Place and Kemptville High Schools and later graduated in Arts and Medicine from Queen's University. After two years postgraduate work on the continent he was appointed Professor of Anatomy at Queen's, a position which he held until 1921. He then took up private practice in Vancouver, where he specialized in surgery. Dr. Kidd spent four years on active service during the First World War, holding the rank of Lieutenant Colonel. He was given the Military Cross and was mentioned in despatches. He served in France and Egypt. He was a Fellow of the Royal College of Surgeons of Edinburgh, Scotland, and was also elected a Fellow of the Royal Anthropological Institute of Great Britain and Ireland, and a Fellow of the American Geographical Society. His work on the huge Indian Midden at Marpole, B.C. was outstanding: and he was an authority on the early Indian osteology of British Columbia. He is survived by one brother and two sisters.

**Dr. R. St. John Macdonald** died in Montreal on September 12. He was in his 68th year. A native of Nova Scotia, he gained his early training at St. Francis Xavier College, Antigonish, then entered McGill University where he obtained an M.D., C.M. in 1903 and his Diploma in Public Health in 1912. He was made a lecturer in that year and assistant professor in 1923. He succeeded the late Dr. Grant Fleming as head of the department. During the First Great War, Dr. Macdonald served as officer commanding the No. 9 Stationary Hospital, Canadian Army Medical Corps. He was tremendously interested in all matters of sanitation, housing and allied subjects. Surviving him are his widow; one son, Ronald; and two daughters.

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**Dr. Michael Joseph McHugh,** who retired only a year ago as superintendent of the Toronto Hospital, Mount Dennis, after 29 years of service to tubercular patients, died on August 27 at his home, in his 58th year. Joining the staff as a medical student in 1918, during the influenza epidemic he was the only medical man on the staff able to remain on duty. On several occasions he took postgraduate courses at various medical centres including Vienna, London, Liverpool, Boston and Chicago. Born in Ireland, he came to Canada in 1913. He received his medical degree from the University of Toronto. He was a past president of Weston Rotary Club. He also served for the past ten years as chairman of the Rotary Club's crippled children's committee. He was a member of the Fourth Degree, Knights of Columbus and of the following medical associations: Academy of Medicine, Toronto; Ontario Medical Association; Ontario Laennec Society; Canadian Medical Association; Canadian Tuberculosis Association; Fellow of the American College of Chest Physicians. He was also a director of the Ontario Hospital Association, director of the Blue Cross Plan for Hospital Care and past president of the Toronto Hospital Council. He is survived by his widow and one daughter, two brothers, and a sister.

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**Dr. David A. MacKay,** a bone specialist on the staff of St. Joseph's Hospital, died August 31. He was in his 48th year. Born at St. George, Ontario, he was educated at Lucknow and Ingersoll schools. He graduated in medicine from the University of Toronto in 1923. After taking a postgraduate course at the Johns Hopkins Hospital for two years he returned to Toronto where he started his practice. He was a member of the Toronto Academy of Medicine and the Canadian Medical Association and the York Downs Golf Club. He was an ardent sportsman and enjoyed hunting and fishing trips. Surviving ar his parents, two daughters, and one son.

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**Dr. Edward William Montgomery,** president of the Canadian Medical Association in 1922, died at Winnipeg on September 27, aged 85. Born in St. Sylvestre, Que., he was educated at Inverness Academy and moved with his parents to Stonewall when he was thirteen. Graduating in Arts from Manitoba College in 1886, he taught at Brandon, then entered upon the study of medicine and received his M.D. degree in 1892. Beginning practice in Winnipeg, he taught continuously from October 1882 to April 1927. When Manitoba Medical College was reorganized as the Faculty of Medicine, University of Manitoba, he became the first Professor of Medicine, and held that position until 1927 when he was elected to the legislature and became the first Minister of Health and Public Welfare, the combination being in itself an innovation. He resigned his teaching post, but was appointed Professor Emeritus of Medicine and received the LL.D. degree from the University of Manitoba.

His ministerial duties were heavy since he had to integrate services formerly administered by other departments and in consequence much legislation had to be introduced. Inspired by the memory of his friend, the late Dr. Gordon Bell, Dr. Montgomery brought to the administration of his department the same qualities of mind and heart which had raised him to leading rank in his profession. Fired with the zeal of a crusader he insisted on a program of immunization of school children which in three years resulted in a reduction of 50% in diphtheria. He was interested in the problem of maternal mortality and established the first health unit in the province. During his term of office, a diagnostic tuberculosis clinic was established in Winnipeg, a tuberculosis sanatorium was opened in St. Vital, the Cancer Relief and Research Institute was set up and modern buildings were erected at Brandon and Selkirk Mental hospitals. A provincial epidemiologist was appointed, and an attempt was made to deal with industrial hazards such as silicosis among miners. To get first hand knowledge of northern Manitoba, he made a trip to Churchill, largely by canoe, and described the rocks and rivers of the North in two articles in the *Manitoba Medical Bulletin* as only a scientist and lover of nature could.

The rough and tumble of parliamentary debate was not congenial to him and he retired in 1932 to the chairmanship of the Board of Health, a post which he held till his death. No account of his life would be complete without reference to his efforts to combat tuberculosis. He was one of the prime movers in the institution about 1908 of the Sanatorium Board of Manitoba; he served as chairman of the Board from 1916-1918, and he remained a member until his death. He was deeply concerned with the high incidence of the disease among the Indians of northern Manitoba. His published writings included Studies in Pernicious Anæmia, Memorial sketches of Gordon Bell and J. W. Good, Maternal Mortality, Tuberculosis in Northern Manitoba, and the first David A. Stewart Memorial Lecture. He is survived by his widow, three daughters and two sons.

Though he had a large and important private practice, his true vocation was public health and his avocation the study of nature. He had a fine garden at his summer home by the Red River, north of Winnipeg and a fruit grove in southern California. A singularly keen and analytical mind and an impelling energy made him a leader in many fields.

### An Appreciation

With the death of Dr. E. W. Montgomery the citizens of Winnipeg have lost a man who was a very outstanding physician and a man of wide knowledge of human affairs. His life was spent wholeheartedly in the service of others, and of him it might well be said "He loved his fellow men". Even at a very early age his keen intellect and outstanding diligence gave promise of a distinguished future, and his long and active career have amply fulfilled that hope. Both at school and at the university he greatly distinguished himself, gained many honours, and easily outdistanced the majority of his fellows.

For many years he carried on a very large general practice, and here his energy and capacity for work were prodigious. His success in practice could not be said to be due to his suavity of manner; if anything he was inclined to be almost abrupt. But he had an abundance of practical common sense and a marked ability to inspire confidence in his patients, who felt that he was giving of his best and that his best was based on the firm foundation of a mind well stored with knowledge, and a heart which emanated kindness. He was never tempted to be carried away by the lure of remedies which were untried and unproved, and whose only virtue was their novelty. In fact his methods of treatment were remarkably simple, and his results correspondingly good. I can well recall a remark made by an intern many years ago, when Dr. Montgomery's patients in the hospital far outnumbered those of any other doctor. In discussing the various doctors and their special lines of treatment, as interns will, one young doctor made the remark "There is no use talking. Monty uses the simplest and most common remedies, but he has more short cuts to good results than any other doctor attending the hospital". To this we all agreed.

I have no doubt that appropriate testimonies to his brilliant career as a physician and teacher will be paid by those who are much better fitted to do so than I am, but as a personal friend of well over half a century I should like to pay my humble and heartfelt tribute to his memory. He was a man of remarkable and delightful character, endowed with outstanding vigour and zest for life and fellowship. My earliest conscious recollection of Dr. Montgomery dates back a long way—to a hot dusty road near Stonewall, Manitoba, where a slight wiry young man could be seen striding energetically along what was about a twenty mile hike, home for a week-end from teaching school. A few years later I had the good fortune to be a pupil of his and I certainly look back on this period as a high-light in my early schooling.

He was a born teacher, and this faculty remained one of his outstanding characteristics. In later years his clinics were always exceedingly practical, interesting and instructive, and as a result were well attended. Apart from his knowledge of medicine, he was an avid reader. He had no great fondness for the modern novel or even the thriller, but any work in science, philosophy or nature study held a strong appeal for him. He dearly loved outdoor life, and his magnificent garden along the bank of the Red River just north of Winnipeg bore testimony to his deep knowledge and love of flowers and plants. He had a keen sense of humour and was a wonderful raconteur. To recall any of the many evenings spent round the camp stove in the fishing or shooting lodge brings back many wonderful memories.

Truly the passing of "Monty" has broken a strong link with the past in many phases of the life of our Province and Dominion.

JOHN A. GUNN, C.B.

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**Dr. Steward Murray** of River John, N.S., died following an operation in Montreal on September 23, 1948, at the age of 56 years. Born at River John, the son of Dr. D. A. Murray and Emma MacKenzie Murray, he graduated from McGill University in medicine in 1921. Returning at once to his native village he assumed the practice carried on by his father for over 40 years. He was regarded as one of the most capable physicians in Pictou County and his practice extended over a wide rural area. At the time of his death he was a member of the Provincial Medical Board of Nova Scotia.

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**Dr. William O'Hara,** aged 66, died on September 28 at his home in Toronto. He had been chief surgeon at Mercy Hospital for a number of years. He had also served as a coroner for the past 15 years, and was known throughout the city for his work among the poor. Born at Hagersville, he graduated from the University of Toronto in 1905. In the words of fellow-medical men, he was "one of the outstanding medical men in the province". Supervising Coroner Dr. Smirle Lawson said Dr. O'Hara's death would be a blow to the poor of the city and to the chief coroner's department. Dr. O'Hara was a member of the Holy Name Society, the Catholic Order of Foresters, the Knights of Columbus and other organizations. Surviving are two sons, two daughters, and one grandson.

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**Dr. George Ross** died in Calgray on September 12, aged 78. Born at Lac St. John, Que., May 19, 1870. Dr. Ross had practised medicine in Alberta since 1920. As graduate of New York University he later did post-graduate work at Chicago University. Dr. Ross received a Ph.D. degree at the University of Illinois and then returned to Canada. Unable to settle down to ordinary practitioner work, Dr. Ross joined the Hudson's Bay Company as a surgeon. He established a post for the company at Seven Islands on the Labrador coast, spending several years in that area. To aid in missionary work among the Indian tribes, Dr. Ross, who spoke at least four tribal dialects, worked in collaboration with the late Bishop R. Rennison in translating Bunyan's Pilgrim's Progress and many Sankey and Moodie hymns into Indian. He saw active service with the Canadian Army Medical Corps in France in World War I. Survivors include four brothers, Art Ross, vice-president and general manager of Boston Bruins of the National Hockey League; Dr. Colin Ross of Montreal; Dr. T. R. Ross of Drumheller, Alta.; Alexander of Sudbury, Ont., one son, Robert of Seven Islands, Labrador, and one daughter, Mrs. Charles Cardin of Montreal.

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**Dr. Thomas B. Stevenson** of Wetaskiwin, died on September 26 at the age of 67. Dr. Stevenson was born in Ontario, graduating from Trinity Medical College in 1904. Following three years in Toronto he came West to practise in Wetaskiwin in 1907. During his active practise over the years he made frequent trips for post-graduate work in the medical centres of the United States. In the latter part of his practice Dr. Stevenson was appointed Medical Health Officer for the city of Wetaskiwin.

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**Dr. Norman Llewellyn Terwillegar** of Edmonton, aged 64, died in hospital August 31, following a heart attack. A native of Oshawa, Ont., Dr. Terwillegar graduated from the University of Toronto in 1909. He first practised in Tofield in 1911 before moving to Edmonton a year later at which time he joined the surgical staff of the Royal Alexander Hospital. He was a former member of the Kiwanis Club and was a Mason. For many years he was an active member of the Royal Curling Club. Surviving are his widow, one daughter, a brother and a sister.

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**Le Dr Joseph-Louis Trudeau,** qui avait pratiqué sa profession pendant 54 ans à S.-Rémi de Napierville et avait été maire cette municipalité à deux reprises, est décéde à son domicile à Montreal le 30 août, à l'âge de 82 ans. Fondateur et président de la commission scolaire de S.-Rémi, il était bien connu pour ses œuvres philanthropiques. Il était né le 5 février 1866, à S.-Michel de Napierville. Après son cours classique au collège de Joliette, il était entré à l'école de médecine du collège Victoria. Il avait reçu son diplôme en 1882, pour aller pratiquer à S.-Remi Il laisse deux fils, trois filles, un frère et trois sœurs.

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**Dr. Robert J. Tucker,** Paisley's only medical practitioner, died of a heart attack on September 23. He was in his 61st year. Dr. Tucker was a native of Ceylon. He graduated from Queen's University in 1916, and served in the First Great War. In 1919 he came to Paisley. He was an elder of Knox United Church here, an Oddfellow and a Mason. He is survived by his widow and three daughters.

# NEWS ITEMS

## Alberta

The Alberta Medical Association held its annual convention in the City of Calgary on September 22, 23 and 24. There was a satisfactory attendance from all parts of the province. A number of fine papers were presented and the round-table conferences were very enlightening. Dr. Gordon Ellis of Edmonton was elected the new President, taking the office over from Dr. A. E. Wilson of Calgary, the latter presenting an original badge of office, beautifully designed, at the inauguration of Dr. Ellis. The Association are very grateful to Dr. Wilson for his originality and kindness in this presentation.

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The excellent fall weather present in Alberta has given the medical men an opportunity to get in some fine shooting since the season was opened and those who desire this sport are well rewarded.

Arrangements are being drawn up for the divisional meeting of the American College of Surgeons which is to be held in the city of Edmonton in the early part of 1949. Dr. McEachern of the College was a recent visitor to the city for the above purpose.

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The new wing of the Lamont Public Hospital was opened on October 4. This most up-to-date addition will be a great asset to the town and surrounding districts of Lamont. Dr. A. E. Archer and his worthy staff are to be congratulated for this great attainment in the field of medical and surgical progress. The Lamont hospital is one of the earliest smaller town hospitals in the province. W. C. WHITESIDE

## British Columbia

Some weeks ago, the daily press recorded a series of "cures" of arthritis by a layman named Green, who was practising near Alberni, B.C. Very strong claims were made for the efficacy of a secret remedy he prescribed, of which he refused to give the formula. A committee was appointed by the B.C. Government to investigate these claims. It included Mr. E. S. H. Winn, K.C., former chairman of the Workmen's Compensation Board; Dr. G. F. Amyot, Provincial Medical Officer of Health; Dr. W. Bagnall, of Vancouver, recognized as an authority on arthritis; and Dr. H. H. Boucher, orthopædist, of Vancouver. These gentlemen interviewed Mr. Green and many of his patients and reported very strongly against the efficiency or value of his treatment. Many so-called arthritics were not arthritics at all, and so on.

Since then the Government has issued an analysis of the "remedy" which shows it to be quite worthless therapeutically. By this wise action, the Government has averted any suggestion of prejudice on the part of the doctors, and has protected the public from quackery. This man has been forbidden to continue prescribing this stuff.

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At the time of writing, the Annual Meeting of the British Columbia Medical Association is in full swing, and a large number of medical men are in attendance. Economic questions are occupying a large share of the time allotted to business, but the scientific aspect of the meeting is the first consideration, and the speakers are all men of high calibre. We have with us too, Dr. William Magner of Toronto, President of the Canadian Medical Association, Dr. T. C. Routley, General Secretary, and the friend of all medical men, and Dr. A. E. Archer of Alberta, consultant on economics.

During the three days of the Annual Meeting, other organizations are holding their special meetings. Among these are the British Columbia Surgical Society, the British Columbia Society of Internal Medicine, the British Columbia Association of Pathologists, and the Eye, Ear, Nose and Throat Society.

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An excellent refresher course in pædiatrics was given during the week of September 23 to 28. The Health Centre for Children in Vancouver was the focus of the course, and the Vancouver General Hospital was the scene of many clinics and lectures. The anæsthetic and pathological staffs of the Vancouver General Hospital, as well as practically all the pædiatricians in Vancouver, took part in this course, and it was a very great success, according to all who attended it. J. H. MACDERMOT

## Manitoba

Dr. and Mrs. William Locke who have been visiting in Winnipeg have left for Boston where Dr. Locke will take an appointment at Harvard Medical School in the Massachusetts General Hospital.

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Dr. M. R. Elliott presided at the graduation exercises of the Central School of Practical Nurses in the Legislative Building on August 27. Dr. Ella Peters, director of the Maternal and Child Hygiene Department, addressed the graduates, and Dr. O. C. Trainor, Chairman of the Advisory Council for Licensed Practical Nurses, presented the licenses.

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Dr. John P. Gemmell, Winnipeg, has been awarded a national research council medical fellowship for postgraduate work. Graduating in 1941 with the highest council medical fellowship for postgraduate work. Graduating in 1941 with the highest honours he served in the R.C.A.M.C., then did postgraduate work in England and at Yale University. He will carry on his research in medicine at the University of Manitoba.

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Dr. J. J. Van Loghem Jr., head of the blood grouping department of the central laboratories for blood transfusion in the Netherlands visited Winnipeg in September to study the blood transfusion service under the Canadian Red Cross. While in the city he was the guest of Dr. S. D. Rusen whom he met during the last war. On September 9 he had lunch with Dr. Bruce Chown, Mr. George Aitken, president of the Manitoba Branch of the Red Cross and Mr. C. H. MacKelvie, chairman of the Manitoba blood transfusion service.

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The building on Osborne Street North, now under construction, and which will house the blood transfusion service of the Red Cross, is expected to be open by late winter.

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The Brandon club of the Associated Canadian Travellers at the banquet meeting on September 10 presented a cheque for $8,500 to the Manitoba Sanatorium Board to be used for the prevention of tuberculosis in the province. This cheque brought the club's donation for the year to $23,000 and boosted the total contribution the club has made since it stated its anti-T.B. projects to $80,000. Most of the money was raised through a series of amateur contests held in towns throughout western Manitoba and broadcast over station C.B.X. in Brandon.

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The Section of Obstetrics and Gynæcology of the Winnipeg Medical Society at the meeting on August 26 appointed a committee under the chairmanship of Dr. Henri Guyot to study the outbreak of mastitis and skin infections due to hæmolytic *Staph. aureus.*

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Dr. Charles Hollenberg, O.B.E., F.R.C.S., who has spent several years overseas with the R.C.A.M.C., has returned to Winnipeg and is engaged in practice with his brothers in the new Hollenberg Clinic building on Graham Ave.

Dr. (Colonel) F. A. B. Sheppard was made Companion of the Order of the Indian Empire at an investure by Viscount Alexander of Tunis, Governor General of Canada at Manitoba's Government House on September 18.

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## New Brunswick

Dr. D. C. Malcolm of Saint John was re-elected grand master of the Grand Lodge of New Brunswick, Free and Accepted Masons, at the 81st annual meeting in August.

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Dr. R. W. Fanjoy has begun practice in Rothesay, New Brunswick.

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Dr. R. W. L. Earle of Perth presided at a well attended meeting of the physicians of Victoria and Carleton Counties on August 30 at Perth. At this meeting Dr. T. E. Nugent and Dr. R. G. Giberson of Bath were nominated as clinicians of a new regional cancer diagnostic clinic to be located at the Hotel Dieu Hospital at Perth. Dr. D. F. W. Porter of Fredericton and Dr. J. R. Nugent, Dr. R. A. H. MacKeen and Dr. A. S. Kirkland of Saint John were outside speakers.

This committee approved the nominations and it was announced that the new clinic would be in operation in about three weeks.

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Dr. B. A. Puddington of Grand Falls is reported to be greatly improved in health following a long, serious illness.

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Dr. Harold Warwick of the Canadian Cancer Foundation lately spent some time in New Brunswick surveying the provincial cancer progress. He met the Minister of Health and the Chief Medical Officer, the Cancer Advisory Committee, and many professional and lay groups, interested in the detection, diagnosis, and treatment of cancer.

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During the annual meeting of the New Brunswick Medical Society at Bathurst, the Defence Medical Association of Canada, New Brunswick Branch held its annual meeting, discussed current topics and passed resolutions to be forwarded to Headquarters at Ottawa, especially stressing the need of informing all physicians of their duties to the state in case of war.

Officers for 1948-49 were elected. *President* — Dr. Paul Melanson of Moncton, *Vice President*—Dr. F. H. George of Saint John.

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Dr. R. A. H. MacKeen of Saint John represented the New Brunswick Department of Health at the opening of the Maritime Depot of the Red Cross National Blood Transfusion service at Halifax.

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Hon. Dr. F. A. McGrand announced the opening of the sixth cancer diagnostic clinic at Moncton on September 15, clinician in charge will be Dr. J. W. Dobson and Dr. J. B. Stewart will be alternate clinician.

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Dr. John A. McLaughlin, chief medical officer of the Workmen's Compensation Board of the Province of New Brunswick attended the convention of the International Association of Industrial Accident Board held in New York in September, and took part in discussions on "Trauma and Heart Disease".

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Dr. Geo. White of Saint John has been elected a Fellow of the Royal College of Obstetricians and Gynæcologists. Dr. White has been a member since 1933. It is announced that Dr. White has been elected to the new Canadian Council of the college to represent the Maritime Provinces.

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The Department of Health of New Brunswick has announced the establishment of a new Division of Dental Health for the province with Dr. Robt. S. Langstroth as director.

A. S. KIRKLAND, M.D.

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## Nova Scotia

The 95th Annual Meeting of the Medical Society of Nova Scotia was held at Keltic Lodge, Ingonish, Nova Scotia, from September 12 to 15 inclusive. Ninety-six physicians registered. Besides a fine scientific section the Society reviewed and adopted a health insurance scheme, which operating under its own act of incorporation will shortly get under way in the Province. The meeting was greatly saddened at the sudden and subsequently fatal illness of Hon. F. R. Davis, M.D., Minister of Health for Nova Scotia, who was attending the sessions.

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Dr. John G. MacDougall, Halifax, has been appointed by the Lieut.-Governor in Council, to the Provincial Medical Board replacing the late Dr. M. G. Burris of Dartmouth.

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We learn that Dr. H. K. MacDonald of Halifax, retiring President of the Medical Council of Canada, delivered a valedictory address at its Annual Meeting which has been warmly commended. In it he paid tribute to the late Sir Thos. Roddick through whose efforts the council came into being, and enjoined its members to maintain a safe and comprehensive standard as its basis of licensure.

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Dr. H. L. Scammell of Halifax has been appointed Registrar and Executive Assistant to the President by the Board of Governors of Dalhousie University.

H. L. SCAMMELL

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## Ontario

The problem of the Rh factor in pregnancy is being met by the hospitals in Toronto by a conjoined plan. This plan was started by the pathologists and obstetricians to obtain information of the frequency of sensitization and its bad effects. It has since been thrown open to all physicians in the city. Each hospital does its own Rh testing, but Rh typing and antibody titre is done at a central laboratory at the Hospital for Sick Children. This lessens the difficulty of obtaining testing sera and subtype sera. Only Rh negative blood specimens or unusual cases are referred to this central laboratory. The physician is notified of the group, the Rh factor and the presence or absence of antibodies. The patient is given a wallet card to carry for emergencies. Husbands are tested and the mother is retested especially at the 7th and 8th month. If antibodies have developed or for any condition noted at birth, the baby is exsanguinated-transfused. The cost to the patient is nominal; the original fee covers all subsequent tests. Part of each fee supports the central laboratory.

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The second annual Brydon award presented to the doctor of the district who has made the most noteworthy contributions to medical and community activities was presented to Dr. W. W. Bartlett of Brampton, Ontario, at the annual meeting of District No. 5 held at Keswick. This award was started two years ago by Dr. W. H. Brydon of Brampton. It is for annual competition by doctors who are members of that District, resident in the counties of Ontario, Peel, Simcoe, and the northern half of York. The winner receives a gold signet ring with five diamonds, engraved with the insignia of the Ontario Medical Association. Dr. Bartlett was a Counsellor for District No. 5, a member of the Board of Directors of the Association and took a great interest in local community service.

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A refresher course in practical ophthalmology and oto-laryngology will be given by the Faculty of Medicine at the University of Toronto, January 24 to 29, 1949.

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Professor H. J. C. Ireton, Department of Physics, University of Toronto and Dr. W. A. Hargan, Director of Radiotherapy at the Thunder Bay Clinic of the Ontario Cancer Foundation have been appointed under the Ontario Cancer Treatment and Research Foundation Act as members of the Advisory Medical Board.

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Dr. B. H. Harper, Moose Factory has been appointed medical officer of health for the locality in the District of Cochrane comprising the Townships of Canfield, Caron, Carroll, Ebett, Horden, Maher, Moose and Parr and Factory Island.

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The Faculty of Medicine, University of Ottawa has announced the following recent appointments: Dr. John B. Ewing, M.D., C.M.(Queen's), F.R.C.S.(Edin.), F.R.C.S.[C.] to be Clinical Professor of Surgery. Until recently he was Surgeon of the Wigan Royal Infirmary, surgeon in charge of the surgical unit of the Warrington General Hospital and Surgeon of the War Memorial Hospital, Newton-le-Willows; Dr. Maurice Murnaghan, M.B., (N.U.I. Dublin), M.S. (*ibid.*),

formerly Lecturer in Pharmacology at the National University of Dublin to be Professor of Pharmacology; Dr. Henri de Saint-Victor, M.D. of Quebec City, Associate Professor of Obstetrics; Dr. Victor Szyrynski, M.B.B.S.(Warsaw) to be Lecturer in Psychiatry; Dr. Eugene Gaulin, M.D., F.A.C.S., of Ottawa to be Professor of Urology; Dr. A. L. Richard, B.A., M.D., of Ottawa to be Professor of Gynæcology; Drs. P. B. Belanger, M.D.C.M.; J. P. Bonfield, M.D., M.R.C.S., L.R.C.P.; F. Coté, M.D., F.R.C.S.(Eng.); A. LeRoque, M.D.; A. Lecours, M.D., F.R.C.S.; and J. A. Tallon, M.D., F.R.C.S. of the Ottawa General Hospital to be Lecturers in Surgery; L. T. Dayshaw, Ph.D. to be Lecturer in Psychology; A. W. Beairsto, M.D. and L. Julien, M.D., to be Clinical Assistants in the Department of Medicine.

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Dr. Anna Miller Loane who graduated from McGill in 1944, interned at the Montreal General and Woman's College Hospitals and who did postgraduate work in London, England, has opened a general medical practice at 310 Bloor St. West, Toronto.

LILLIAN A. CHASE

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## Prince Edward Island

During the past summer a series of dinner meetings have been held at the Charlottetown Hotel, which have been extremely popular and well-attended. Dr. Wallace Graham of Toronto was the speaker at the first meeting, speaking on Arthritis, and the work of the Canadian Rheumatism Association. Dr. J. C. Luke of Montreal spoke at the meeting early in June upon "The Treatment of Venous Thrombosis in the Lower Extremities". At the July meeting Dr. H. B. Atlee of Halifax was the speaker, whose topic was "Chronic Pelvic Pain in Women". The final dinner in this series was addressed by Dr. Norman Wrong of Toronto, who spoke on "Recent Advances in the Treatment of Common Skin Disorders". These papers have all been extremely helpful.

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The tenth annual meeting of the Prince Edward Island Division of the Canadian Medical Association was held on Friday, September 10, with forty-six members in attendance. The President, Dr. Henry Moyse, was in the chair. Matters of routine business were discussed. The appointments of Dr. W. J. P. McMillan and Dr. W. B. Howatt as representatives of the Society upon the Advisory Committee set up by the government to deal with matters of public health were ratified. Dr. McMillan spoke in detail about the work of this body. As a result of considerable discussion upon this topic the resolution was passed urging the government to separate the departments of Public Health and Welfare, and to appoint a Deputy Minister of Public Health who is to be a medical man.

The following slate of officers was elected for 1948-49: *President*—Dr. R. G. Lea; *Vice President*—(Prince) Dr. R. Grant, (Queens) Dr. W. Tidmarsh, (Kings) Dr. A. McDonald; *Secretary*—Dr. H. Pierce; *Treasurer*—Dr. J. W. McKenzie.

The C.M.A. party who attended the meeting spoke upon business and clinical matters. Dr. W. Magner, President of the Canadian Medical Association, and Dr. Art. Kelly, Secretary, spoke in detail about the problems confronting the Canadian Medical Association, and Dr. Magner also gave an address on "The Interpretation of Jaundice". Dr. J. W. McNally of Montreal spoke upon "Dizziness", and Dr. Adrian Anglin of Toronto gave two papers, the morning one on "The Management of Rheumatic Heart Disease" and at the afternoon session he spoke upon "The Management of Bronchial Asthma". Dr. H. O. Warwick, Secretary of the Canadian Cancer Institute, was present, and spoke briefly at luncheon upon the work of that organization.

R. G. LEA

## Quebec

Montréal a reçu le 29 septembre un grand neuropsychiatre français, le docteur Paul Delmas-Marsalet, de la Faculté de médecine de Bordeaux. Grâce à une bourse de la Rockefeller Foundation, le professeur Delmas-Marsalet, à qui la convulsion-thérapie des psychoses doit tant, passera trois ans d'observation et d'étude aux Etats-Unis et au Canada.

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Montréal est également l'hôte d'un autre représentant distingué de la médecine française, le professeur Pierre Lépine, directeur du Service des virus à l'Institut Pasteur de Paris. M. Lépine est chargé cet automne d'un cours sur l'épidémiologie des maladies à virus, sous les auspices de l'Ecole d'hygiène de l'Université de Montréal.

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Les docteurs François Cloutier et Georges Saulnier, diplômés de l'Université Laval, seront boursiers du Gouvernement français en 1948-49.

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Le docteur Jacques Genest, ex-chef interne de l'Hôtel-Dieu de Montréal, puis médecin du Johns Hopkins Hospital, a été nommé membre résident du Rockefeller Institute for Medical Research à New-York.

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La Province de Québec est représentée au Congrès international de Médecine industrielle, tenu à Londres, par M. J.-A. Vidal, professeur agrégé à l'Université de Montréal et président de la Commission de la silicose. Le docteur Vidal fera également la visite des centres français d'étude de la silicose.

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The 105th annual meting of the American Psychiatric Association will be held in Montréal in May, 1949. The local Organization Committee will be headed by Dr. Travis E. Dancey, and Professor Emile Legrand will act as vice-president.

PAUL DE BELLEFEUILLE

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## General

The Department of Psychiatry at McGill University is expanding its courses of training for postgraduate students in psychiatry in order to meet the increased demand for such training arising from the establishment of Dominion Provincial health grants. These courses are designed to provide, through the various teaching hospitals affiliated with the University, a general preparation for all aspects of the psychiatric field. In addition, arrangements can be made for the student to devote special study to any aspect of the field in which he has a primary interest, such as, community psychiatry, general hospital psychiatry, psychotherapy, research procedures and methods, or intensive therapy of earlier cases, as well as to problems of continued care of institutionalized patients.

The qualifications for admission to the courses are: (*a*) A degree from an approved medical college, or school. (*b*) A general internship of one year's duration. (*c*) A satisfactory personal interview, or where this is impossible, adequate recommendations.

The following courses have been set up: (*a*) The Four Year McGill Diploma Course. (*b*) Courses of a general nature, ranging from periods of one to four years. (*c*) Courses of special instruction to be arranged through discussion with the Departmental Committee.

Further information concerning the courses, concerning application and fees, may be obtained by writing to the Chairman of the Department of Psychiatry, McGill University, Montreal, Que.

Courses of instruction have also been organized for psychiatric social workers and for graduate students in psychiatric nursing. Information concerning these courses may be obtained by writing to the McGill School of Social Work and the Graduate School of Nursing at McGill respectively.

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In our September number, p. 301, announcement was made of *Medicine of the Year*, the annual review of medical progress offered to our members as a supplement to our *Journal*. For the benefit of those members who may have failed to notice it, or as yet failed to subscribe, the announcement is repeated in this issue of the *Journal* in the belief that the review contributes a valuable educational opportunity at little cost. Recent information from the editorial office of *Medicine of the Year* indicates that the plan for the review is proving popular in the States where it has already been announced. Additional States are planning announcements soon. Recently the associate contributors for the various medical specialties, a group of distinguished authors and nationally known authorities in their fields, have been selected. They are the following: Allergy—Dr. Harry L. Alexander; Pulmonary Disease—Dr. J. Burns Amberson; Metabolism and Endocrinology—Dr. Kendall Emerson, Jr.; Dermatology—Dr. Chester N. Frazier; Cardiovascular Diseases—Dr. William J. Kerr; Neurology—Dr. H. Houston Merritt.

In order to provide this service, it is necessary that a minimum number of subscriptions be entered and each member is urged to send in the coupon without delay. No obligation is incurred if an insufficient number is secured and if an adequate number is secured you can be assured of a valuable aid at nominal cost. Subscribe now.

## BOOK REVIEWS

**British Surgical Practice.** Under the General Editorship of Sir Ernest Rock Carling, Consulting Surgeon, Westminster Hospital; and J. Paterson Ross, Surgeon and Director of Surgical Clinical Unit, St. Bartholomew's Hospital. Vol. 1, 486 pp., illust. Vol. II, 589 pp., illust. Butterworth & Co. (Publishers), Ltd., London; Butterworth & Co. (Canada), Ltd., Toronto, 1948.

In their introduction, the editors state that the work is written for those surgeons who do not have ready access to libraries. It is intended neither for the expert nor for the undergraduate student, "though many of the articles written with the simplicity, which none but masters can achieve, will not prove too difficult even for the beginner". The general editors accept responsibility for what appears in these volumes, but having chosen their man, they allow him to express his preferences without undue interference. The first two volumes fully live up to this preface. One or two references only will be made.

"Abdominal Pain" by J. H. Kellgren is a readable summary of his findings while working with Sir Thomas Lewis. He used injections of 0.1 c.c. of 6% saline which produced a pure, severe pain comparable with that of disease. The pain symptom complex is discussed and "the deep tender spot" is defined and exemplified. It is unexpected to find such topics as Appetite, Asymmetry and Adiposity, but these short interesting articles add balance to the work. All the usual subjects are here, such as the Abdominal Wall, Abortion, Abscess and Adhesions, the latter considered both from the abdominal and chest aspects. The article on Acute Appendicitis gives a clear classification of this condition, and is improved by dividing the indications for surgical intervention into early and late, with the third day as the dividing time. In this delightfully complete résumé, the author compares immediate operation with conservative treatment. The essay on "Tumours of the Appendix" contains a wealth of information in a compact space.

The second volume is largely taken up with special subjects including the Bladder, Bones and Brain. The bladder is discussed under headings of infections, injuries, neurogenic disturbances, pouches and tumours. The section on bones is very thorough and includes bone grafting, acute and chronic infections, errors of development and growth, and metabolic dystrophies. Many pathological rarities are included, but this does not detract from its usefulness. The greater part of the section on brain surgery is devoted to practical applications. Dr. K. G. McKenzie is the author of brain abscess and Dr. E. H. Botterell wrote the section on injuries and complications. The section on Carcinoma of the Breast, one of those areas still left to the general surgeon is shorter and less detailed than the preceding articles. No mention is made of grading malignancy which seems a serious omission. However, the conclusions on treatment are a balance between the extremes on the United States and on the Continent. These two first volumes make a sound summary of British surgical practice. "British" is used in the wider sense, meaning the British Empire, for the consultant editors are from Canada, Australia, India, South Africa, as well as the British Isles. The methods of classification and indexing are particularly valuable for those preparing lectures for the higher degrees, as well as those candidates who have to cover a large field in a short period of time. They also make a useful reference library for those in isolated areas, such as mining communities or at sea.

**Delayed Union in Fractures.** K. W. Starr, Surgeon, Sydney Hospital, New South Wales. 248 pp., illust. $12.50. Butterworth & Co. (Publishers), Ltd., London, Eng., and Toronto, 1947.

The author has made a very capable, extensively scientific and practical presentation on the subject of delayed union in fractures. The histopathology and chemical aspect of union of fractures has been exceptionally well treated. His statements are dogmatic and well supported by clinical evidence. In fact the subject of fractures has been beautifully traced from the days of the Egyptian up to and including the modern era. Conservatism in fracture treatment is recommended provided careful assessment is made immediately. Those assessed as likely to predispose to delayed non-union are treated radically immediately. Repeated closed manipulation is not recommended as it predisposes to non-union. Radical open operation is suggested in the early days of the first week of fracture in such cases. Of interest in open reduction of fractures is the use of non-absorbable sutures, wires, plates, screws and sliding bone grafts, supported by intensive drilling of the compacta of the diaphysis and compacta of the graft. Circulation in region of fractures is improved by daily passive congestion up to discharge of patients by sympathectomy. Chemotherapy is recommended pre- and post-operatively in conjunction with careful surgical principles, in the form of sulfadiazine and later 5-amino acridene and penicillin.

This essay is well worth careful consideration and digestion by surgeons interested in traumatic surgery.

**Wayfarers in Medicine.** W. Doolin, Editor of the *Irish Journal of Medical Science*. 284 pp., illust. 21s. Messrs. William Heinemann Medical Books Ltd., London, 1947.

This book is still another example of the fine medical literature dealing with medical history which is being written in these times. So much of the work in this field is as flat and featureless as an arid plain. It is therefore refreshing to come upon a writer who combines scholarship and erudition with literary charm and the power to evoke the past. These essays are the work of Mr. William Doolin, a Dublin surgeon who is also the editor of *The Irish Journal of Medical Science*, and provide a panorama of medical history from Imhotep to

Robert Jones. With a sense of historical colour, fine dramatic tension, wide allusion and lively humour, there is built up a pageant which the reader, whether versed in medical history or not, must find compelling.

Some of the chapters—each a finished essay which looks before and after, thus providing fascinating vistas—are particularly notable. These deal with John of Arderne, Benvenuto Cellini, Montaigne, the early Edinburgh surgeons, and (as one would expect) the great names of the Dublin School. Mr. Doolin's gifts as a writer can probably best be appreciated by seeing how he handles such much-written-of celebrities as Harvey and Ambroise Paré. There are interesting chapters well out of the worn paths of medical history dealing with the anatomist in art, old journeymen surgeons portrayed in pictures and prints, and urinary calculi as set out in literature and art. For the bookmen there is a section at the end of the volume giving bibliographical notes which are of great interest. And one should mention the charming dedication to Dr. Kirkpatrick which reflects the high fellowship of medicine.

This is a book to hearten those who at times despair of medical culture, to entice the diffident novice into the field of medical history, and to give pleasure to all who enjoy the flavour of good writing in whatever sphere.

**Concise Anatomy.** L. F. Edwards, Professor of Anatomy, the Ohio State University, Columbus, Ohio. 548 pp., illust. $6.25. The Blakiston Co., Philadelphia and Toronto, 1947.

This revised form of the book previously published as Anatomy for Physical Education will be welcome to teachers of anatomy who are concerned with the instruction of students in the various ancillary fields of medicine such as physical education and physiotherapy. While the actual form and text of this book may not be directly applicable to some of these courses, the arrangement is such that it is a simple matter for the teacher to supply his own deletions or abridgements. The text is arranged in both systematic and regional forms so that either procedure may be followed in instruction. In addition, there is an excellent section on general anatomy and throughout the book a happy interweaving of gross and microscopic structure.

**Noah Webster: Letters on Yellow Fever Addressed to Dr. William Currie.** Supplements to the *Bulletin of the History of Medicine*, Editor Henry E. Sigerist, Associate Editor Genevieve Miller, No. 9. 110 pp. $2.00. The Johns Hopkins Press, Baltimore 18, Maryland, 1947.

This is another of the interesting monographs published under the direction of the *Bulletin of the History of Medicine* and under the inspiration of the Institute of the History of Medicine in Baltimore. For those interested in American history these letters reveal the capacity and breadth of mind of Noah Webster, whose fame as a lexicographer has overshadowed his contribution to medical literature. For students of medicine they show the value of an approach to medical problems by an independent and philosophical mind and how sorely medicine needs such scrutiny. Webster is seen as one of the original modern thinkers in the field of epidemic disease, speculating boldly on the concepts of contagion and infection, stressing the value of statistics and forwarding the idea of public education in matters of health. In his analysis and criticism of medical problems and theories, Webster makes the same effective and versatile approach as Franklin, Jefferson and other lay thinkers. Dr. Spector prefaces his collection of these letters with an admirable commentary on Webster and the social and medical world of the time.

**Background of Therapeutics.** J. H. Burn, Professor of Pharmacology in the University of Oxford. 367 pp., illust. $6.75. Oxford University Press, London, New York, Toronto; McAinsh & Co., Ltd., Toronto, 1948.

This is a very well conceived book designed especially for clinical teachers and provides, as the title indicates, the rationale for some of the newer therapy. The historical background of pharmacology is presented in an introductory chapter dealing with systems of medicine and a plea is made for teaching pharmacology in the clinical years of the medical curriculum. The rest of the book is made up of 16 chapters devoted to the principles of treatment in various disorders. These include discussions on hypothalamic function, thyroid activity and hypertension, allergy and the antihistamine drugs, obesity, chemotherapy in syphilis, malaria and the bacterial diseases, acetylcholine and the myasthenias and the use of the newer analeptic and pressor drugs. There is an extremely practical chapter on the process of disinfection which every practitioner should read. The section dealing with anæsthetics is written with H. G. Epstein and presents a clear and concise account of the modern concepts in this field. The final chapter headed "Statistics Explained" is especially welcome. This is a clear presentation of some of the fundamental features in this field for the worker whose need for statistics is occasional. No special mathematical knowledge is required to follow the directions given for obtaining standard deviation, standard error and significance. This book should be consulted by every clinical teacher and can be recommended especially for senior students.

**Diagnosis and Treatment of Menstrual Disorders and Sterility.** C. Mazer, Assistant Professor of Gynæcology and Obstetrics, Graduate School of Medicine, University of Pennsylvania; and S. L. Israel, Instructor in Gynæcology and Obstetrics, School of Medicine, University of Pennsylvania. 570 pp., illust., 2nd ed. $7.50. Paul B. Hoeber, Inc., New York, 1946.

This is a clinical text intended to meet the requirements of the general practitioner and as such concerns itself chiefly with diagnosis and treatment. These practical aspects are presented very clearly and are based on the authors' personal experiences as gynæcologists to the Mount Sinai Hospital in Philadelphia. Many theoretical aspects such as the consideration of antihormone effects are presented in excellent critical fashion. Diagnostic methods which have been found practical as office procedures are described in detail as are also the therapeutic measures recommended. The book contains many useful tables to show the relative potency of various œstrogens, statistics on the roentgen ray treatment of amenorrhœa, differential diagnosis between primary and secondary ovarian failure and between adrenocortical adenoma and other forms of Cushing's Syndrome. The section on male sterility is well conceived and organized. The text is suitably illustrated and each chapter is followed by a carefully selected bibliography. An appendix of commercially available standardized endocrine products is included. This book is recommended as a guide to the family physician who is first to see and treat the many women suffering from menstrual disorders and sterility.

**Diagnosis and Treatment of Pulmonary Tuberculosis.** M. J. Stone, Assistant Professor in Medicine, Boston University School of Medicine, and P. Dufault, Superintendent of the Rutland State Sanatorium, Rutland, Mass. 325 pp., illust. $4.00. Lea & Febiger, Philadelphia; Macmillan Co. of Canada, Toronto, 1946.

This small volume covers briefly our present knowledge of the pathology, diagnosis and treatment of pulmonary tuberculosis. Following each chapter there is a bibliography showing books which can be consulted for fuller discussion of the subject. Although condensed, it covers the field adequately and should be of value to students and general practitioners.

## BOOKS RECEIVED

**A-B-C's of Sulfonamide and Antibiotic Therapy.** P. H. Long, Professor of Preventive Medicine, the Johns Hopkins University School of Medicine. 231 pp. $3.85. W. B. Saunders Co., Philadelphia and London; McAinsh & Co. Ltd., Toronto, 1948.

**A Way to Natural Childbirth.** H. Heardman, Diploma Bedford Physical Training College. 124 pp., illust. $2.00. E. & S. Livingstone Ltd., Edinburgh; Macmillan Co. of Canada, Toronto, 1948.

**Battle of the Conscience.** E. Bergler, M.D. 296 pp. $3.75. Washington Institute of Medicine, Washington, D.C., 1948.

**Care of Tuberculosis in the Home.** J. Maxwell, Physician to the Ministry's Mass X-ray Unit. 113 pp., illust., 2nd ed. 7/6d. Hodder & Stoughton Ltd., London, 1947.

**Chemistry in Nursing.** R. E. Neal, Associate Professor of Chemistry, Simmons College. 564 pp., illust. McGraw-Hill Book Co., Inc., New York, Toronto, London, 1948.

**Chirurgie de la Surdite.** J. Salomon Danic, Ancien interne des Hôpitaux de Paris. 112 pp. 250 Fr. L'Expansion Scientifique Française, 23, rue du Cherche-Midi, Paris (VIe), 1948.

**Clinical Picture of Thyrotoxicosis.** P. McEwan, Honorary Consulting Surgeon to the Bradford Royal Infirmary. 127 pp., illust. 15/-. Oliver & Boyd, Edinburgh and London, 1948.